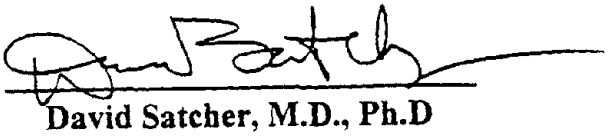
REPORT TO CONGRESS

HEALTH EFFECTS OF DIESEL FUMES ON WORKERS IN UNDERGROUND MINES

Department of Health and Human Services
Centers for Disease Control and Prevention



David Satcher, M.D., Ph.D
Director
Centers for Disease Control and Prevention

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HEALTH EFFECTS OF DIESEL FUMES ON WORKERS IN UNDERGROUND MINES

Background

The Senate Appropriations Report 105-58, accompanying S. 1061, the bill making appropriations for the Departments of Labor, Health and Human Services, and Education for fiscal year (FY) 1998, requested that the National Institute for Occupational Safety Health (NIOSH), Centers for Disease Control and Prevention (CDC), submit a report responding to six questions regarding a multiyear study jointly funded by NIOSH and the National Cancer Institute (NCI), National Institutes of Health, to investigate the health effects of diesel fumes on workers in underground noncarbon mines.

Specifically, the Senate report requested that NIOSH submit a report by December 1, 1997, detailing the following:

1. The extent to which time has been given for public comment on the draft study protocols;
2. The extent to which the study protocols have undergone peer review;
3. The makeup of the review group and the extent to which labor and industry were represented;
4. The extent to which modifications have been made to the study protocols which resulted from recommendations from the review process and/or public comment;

5. Whether any feasibility study has demonstrated the effectiveness of the study equipment, protocol, and design, particularly with regard to the accuracy of historical diesel exposure assessment; and
6. The extent to which data will be shared with participating organizations as it is collected.

The following is NIOSH and NCI's joint response to these issues:

1. The extent to which time has been given for public comment on the draft study protocols.

The agencies provided two extended periods for oral and written public comment during the two- year period in which this protocol was being peer-reviewed. During the initial peer review of the protocol by a panel of outside experts, the agencies provided an opportunity for the public to comment over approximately a three-month period from September 20, 1995, to December 11, 1995. In November 1996, a group of mine owners, the Methane Awareness Resource Group (MARG), filed suit challenging this peer-review process, and a court enjoined any further meetings of this outside peer-review panel. As a result, the agencies decided not to use either the peer review or the public comments received during this peer-review process and initiated a new peer review of the protocol by NIOSH's Board of Scientific Counselors (BSC).

During the peer review by the BSC, the agencies again provided an opportunity for public

comment. This review occurred over the course of three meetings (January, April, and July 1997) of the BSC, and at each of these meetings, the public was provided the opportunity for oral and written comment. The comments of the public, as well as the comments of the BSC, were addressed by the agencies.

2. The extent to which the study protocols have undergone peer review.

The protocol was subject to extensive peer review within each agency. As noted above, there were also two rounds of external peer review, lasting about four months and seven months, respectively. The first peer review panel, composed of experts in epidemiology, industrial hygiene, statistics, and biomarker studies, supplied extensive comments on the first draft protocol (Attachment A). However, as stated above, that peer review was challenged on procedural grounds by MARG as being inconsistent with the requirements of the Federal Advisory Committee Act, 5 U.S.C. App. 2, (FACA). Subsequently, NIOSH and NCI were enjoined by a Federal district court from holding any further meetings of this peer-review panel. As a result, NIOSH and NCI set aside that review and charged a chartered FACA committee, NIOSH 's BSC, which includes national experts in epidemiology, industrial hygiene, occupational medicine, and other disciplines from industry, labor, and academia, with peer review of the first draft protocol. As previously stated, the BSC review took place at three successive meetings of the BSC in January, April, and July of 1997.

In an October 15, 1996, *Federal Register* notice, NIOSH and NCI requested public comments

regarding the scientific and technical merit of the study. That notice and the January 1997 BSC review resulted in extensive written and oral comments by the BSC and the public, which were summarized and responded to by the two agencies in an attached report (Attachment B). At the BSC meeting in April 1997, these responses were considered by the BSC and further written and oral comments were offered by the BSC and the public. The agencies' responses to these further comments were summarized (Attachment C) and presented at the July 1997 BSC meeting

The protocol was revised and modified based on the comments received from the BSC and the public (Attachment D). This revision included major changes from the initial drafts, especially to the exposure-estimation component of the study. The revisions were so extensive that the length of protocol almost doubled, from 55 to 93 pages. This revised protocol was presented at the July 1997 BSC meeting and was approved by all ten of the BSC members in attendance.

3. The makeup of the review group and the extent to which labor and industry were represented.

Attachment E includes the list of the members of the BSC. The committee is currently made up of 13 members (15 authorized), of whom one is affiliated with industry and one with labor, and the remainder are drawn from academia, a professional association, state government, or private consulting.

4. **The extent to which modifications have been made to the study protocols which resulted from recommendations from the review process and/or public comment.**

Attachment B, which consists of 50 pages of responses to the issues raised at and following the January 1997 BSC peer review, details each point and its associated reply by the research team. Page 4 of the attachment lists the major changes to the protocol that were made as a result of the comments by the BSC and the public. There were 11 major modifications, including rewriting of the protocol for exposure assessment component of the project. Pages 5 - 8 summarize the overall impressions of the peer reviewers. Their comments demonstrate that the reviewers considered the study to be important and the methods to be generally, scientifically acceptable. Pages 13 - 50 cover each detailed issue and its response. Attachment C, which consists of eight pages of responses to the issues raises at and following the April 1997 BSC peer review, details each issue raised and the reply by the research team.

5. **Whether any feasibility study has demonstrated the effectiveness of the study equipment, protocol, and design, particularly with regard to the accuracy of historical diesel exposure assessment.**

This study consists of a standard epidemiologic design, and does not invoke any major departures from typical research techniques and practices. Study designs like this are the staple of epidemiologic research in the occupational arena, and thus pose few novel problems

for the researchers. Consequently, there would not be any overriding need for a feasibility study to demonstrate the potential for the study approach to be successful.

However, a feasibility study was undertaken to identify mines of particular utility for the research objectives of the main study. The feasibility study also allowed testing of the proposed industrial hygiene (IH) methods, including IH sampling at one of the mines. The methods used included only those currently contained in the NIOSH Manual of Analytical Methods. The results showed not only that reliable information could be collected, but that there was a high likelihood that accurate assessments of historical exposures could be ascertained.

6. The extent to which data will be shared with participating organizations as it is collected.

NIOSH and NCI are dedicated to the principle of providing access to research data. The reanalysis of research data by researchers with new hypotheses keeps science vibrant and strong. In providing access to data, NIOSH and NCI must, however, balance conflicting rights and responsibilities. These include the right of the public to access information held by the government, a concept embodied in the Freedom of Information Act; a basic right of the individual to privacy, embodied in the Privacy Act; a basic health professional tenet of protecting confidential information; and adherence to the confidentiality restrictions placed by the States and other Federal agencies in providing data that is essential for prevention

research. Accordingly, NIOSH and NCI will release a microfilmed copy of records that we obtain from each company back to that company, will ensure that proprietary information will not be conveyed to third parties, and will ensure that research data will be available once the data set has been finalized to ensure accuracy and that its release does not divulge personal and confidential information. This approach has been successfully employed for decades of research into the prevention of occupational injury and disease by both NIOSH and NCI.

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A Summary of Comments and Responses from the Peer Review of the Study Entitled

"A Cohort Mortality Study with a Nested Case-Control Study of Lung Cancer and Diesel Exhaust among Non-metal Miners"

held on November 27, 1995 in Washington, DC

September 23, 1996

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INTRODUCTION

The following is a summary of responses to questions and comments submitted in writing to the project team for the study, "A Cohort Mortality Study with a Nested Case-Control Study of Lung Cancer and Diesel Exhaust among Non-metal Miners" for the Peer Review held on November 27, 1995.

General comments

Written comments were received from each Peer reviewer, from several individuals connected with industry and the coalition of mines, and from one governmental institution. The importance of the study was acknowledged by most who submitted comments. One industry affiliated individual noted, "This study will potentially become the definitive study upon which future risk assessments will be made and may ultimately become the basis of regulatory exposure limits." Comments from the Peer panel members were generally very favorable towards the overall concept and design of the study. Statements such as, "This proposed study is an excellent example of a well developed, collaborative, interagency study...," and "..on the whole the proposal is well thought out..." were received. Nevertheless, many suggestions for improvements, comments, criticisms, and were submitted, in addition. The following text provides responses to the issues raised, first in summary, and then in detail.

Summary of responses to the main issues

These are summarized according to each section of the protocol.

1. Summary.	No major questions. (Two important points raised concerning the biomarker and exposure assessment components are dealt with in sections 7 and 8.)
2. Background.	No major questions. (Contradictory points were raised about the summary of findings; consequently no change was made.)
3. Feasibility study.	No major questions. (Some misunderstandings and ambiguities concerning the feasibility study have already been discussed and clarified at a meeting of the Exposure Assessment Work Group. See Section 5 for criteria for record completeness.)
4. Study objectives.	These have been modified slightly for clarity.
5. Cohort study.	Mine selection. More information was requested on the criteria for mine selection, and this has been given (now in Appendix B).
	Study design. Various questions were raised concerning the study design. In response, the criteria for inclusion in the study were changed, office workers were removed from the unexposed control group, and county reference mortality rates were dropped from the analysis.
	Smoking. Concern was expressed about the quality of information on smoking, and the potential for confounding between smoking and exposure. In response, it was pointed out that the quality of smoking information is

probably better than in most cohort studies, that confounding between smoking and exposure has not been found to be a severe problem in occupational epidemiologic studies, and that steps will be taken to adjust for smoking. In addition, the findings from the cohort and case-control study (where smoking information will be available) will be compared for consistency in relation to potential smoking-related effects. No major changes to the protocol.

Confounding exposures. In a related issue, concern was raised about confounding from other exposures received prior to, during, or after, work in the study mines. In response, it was noted that confounding exposures at the study mines are believed to be inconsequential, though check samples will be taken, and the statistical models adapted as appropriate. Exposures prior to work in the study mines will be ascertained from information abstracted from pre-employment forms and additional model terms included in the models as appropriate. Some proposals for dealing with exposures received after leaving the study mines are included in the protocol (5.D.2). As was stated above,for smoking, the internal consistency between the cohort and case-control studies will provide information towards assessing any difficulties with confounding from other exposures in the cohort study.

6. Case-control study.

Interviews on case surrogates and controls. Various points were raised concerning the validity and comparability of data from case surrogates and controls. Responses to these are provided. The proposed procedures follow standard practice. No major changes to the protocol.

Reliability of information on diet and pesticide exposures. Concern was expressed that data on diet and pesticide exposures may not be reliable. In response, it was noted that the dietary questions were simple and mainly pertained to fruit and vegetable consumption. The pesticide questions were removed (6.C.1).

Matching ratio. The decision to use four controls per case was questioned. In response, it was noted that the ratio has been reduced to three to one (6.B.2).

Blinding of interviewers. In response to questions about blinding of interviewers to case-control status, the wording of the protocol has been modified to make this more explicit (6.C.2).

8. Biomarker study.

Justification for biomarker study. Concern was expressed about the need and justification for the biomarker study. Aspects of the protocol dealing with this topic have been expanded to make clear the desirability of this study component, particularly in relation to its utility with respect to interpretation of the findings from the cohort and case-control components. The biomarker study will now be found to be much more tightly linked with the epidemiologic components (7.A and 7.B).

Specificity of nitro-PAH DNA adducts. In response to concerns about the specificity of nitro-PAH DNA adducts, it was noted that account of potential

sources of nitro-PAH will be undertaken in analysis .

Exposure assessment. Following comments, the exposure assessment aspect of the biomarker study was extensively revised to tie it in more closely with the expected biological kinetics of excretion, metabolism, and adduct formation (7.D and 8.E).

2. Exposure Estimation. The proposed exposure zone plan for estimation of worker exposures was questioned by several individuals. In response, this section has been completely rewritten to reflect a more conventional approach based on job-exposure matrix principles.

DETAILED RESPONSES

The comments are organized according to the different parts of the protocol, and include sections on the Summary, Background, Feasibility Study, Study Objectives, Cohort Study, Case-Control Study, Biomarker Study, and Exposure Assessment.

Each entry consists of a quotation or precis of the issue raised, followed by a response. In some cases, related points are grouped and one response given to all. The following individuals, groups, or institutions provided written comments; in the text, each comment is prefixed with the indicated abbreviated name for brevity. Please note that page, paragraph, and section numbers refer to the August 9, 1995 version of the protocol.

Abbreviated Name	**Full Name and Source**
Corn/Cole/Mandel	A combined report by Drs. Philip Cole, Morton Corn, and Jack Mandel.
Gibbs	Dr. John Gibbs, Kerr-McGee Corporation.
Hathaway	Dr. James Hathaway, Rhone-Poulence Corporation
Howard	Mr. Howard, Mine Safety and Health Administration.
O'Toole	Mr. Michael O'Toole, USG Corporation.
Redmond	Dr. Carol Redmond, University of Pittsburgh and Peer Reviewer.
Santella	Dr. Regina Santella, Columbia University and Peer Reviewer.
Schenker	Dr. Marc Schenker, University of California at Davis and Peer Reviewer.
Seixas	Dr. Noah Seixas, University of Washington and Peer Reviewer.
Shy	Dr. Carl Shy, University of North Caroline and Peer Reviewer.
Steenland	Dr. Kyle Steenland, NIOSH.
Woskie	Dr. Susan Woskie, University of Massachusetts at Lowell and Peer Reviewer.

SECTION 1 - SUMMARY

Corn/Cole/Mandel

Comment: "The paragraph is somewhat ambiguous in its use of the word "risk" followed by a statement regarding the need for information on the "quantitative relationship." The erroneous implication is that there is an established causal relationship for which only exposure-response information is lacking when, in fact, the causal nature of the association has not been established. (Page 4, para. 2)

Response: On page 4, paragraph 2, it clearly states that "the risk of lung cancer in humans is still not well defined." Consequently, it is perplexing to us how this could be interpreted as implying that a causal relationship has been established. The sentence was reworded to avoid such an interpretation.

Cole/Corn/Mandel

Comment: "A reference to the IARC categorization of diesel exhaust should be included. The information available does not indicate that IARC has classified diesel exhaust in category 2B. Further, the National Toxicology Program does not list diesel exhaust even as a suspect carcinogen. (Page 4, para. 2)

Response: Both in the summary and elsewhere we say that IARC has classified diesel exhaust as a probable carcinogen (which is a 2A (probable) not a 2B (possible) classification). The point of the paragraph was not to list every organization which does and does not list diesel exhaust as a carcinogen, but to make the point that despite certain current authoritative statements, further information is still necessary.

Cole/Corn/Mandel

Comment: "A first reference is made to the biomarkers study. But neither here nor elsewhere is the need for such a study developed adequately. (Page 4, para. 3)

Response: It is now considered that biomarker components are desirable adjuncts to mortality studies (Harrington, Pre-proceedings of International Seminar on Assessment of Carcinogenic Risk from Occupational Exposure to Inorganic Substances, Luxembourg, 1995). See below for responses specific to the biomarker component.

Cole/Corn/Mandel

Comment: "The exposure assessment proposed as a feasibility study requires validation. In view of the concerns expressed later in this report, it would seem prudent to resolve the issues before proceeding with the study.

Response: This issue has already been dealt with by the Exposure Assessment working group.

Cole/Corn/Mandel

Comment: "Why not wait to see if diesel exhaust is, in fact, associated with lung cancer before starting the biomarker study?" (Page 5, para. 3)

Response: We gain efficiency in the study by doing the biomarker component at the same time as the mortality study. Moreover, having the results of the biomarker study at hand when the findings from the mortality study are complete will enable the implications of each to be interpreted better. See specific biomarker responses for further justification.

SECTION 2 - BACKGROUND

Cole/Corn/Mandel

Comment: "The investigators should address the naturally occurring dusts in the mines in addition to the sources for elemental carbon either through the mining of the ore or through the use of explosives whose by-products may compound the exposure assessment." (Page 6)

Response: Page 6 is concerned only with diesel exhaust exposures, their composition, and their effects. It was not the intent at this stage to mention specific environments, elemental carbon, nor other dusts. The point raised is legitimate, however, and is addressed in the IH section.

Experimental evidence

Hathaway

Comment: "The protocol should mention that whole diesel particulates are not

mutagenic in bacterial systems. Only organic solvent extracts are mutagenic."

Response: This statement is incorrect. NIOSH researchers have shown that in vitro surfactant-dispersed diesel soots are mutagenic, without solvent extraction, thus showing that genotoxic hydrocarbons associated with diesel soot are biologically available (Wallace et al., Mutagenicity of Diesel Exhaust Soot Dispersed in Phospholipid Surfactants in *Environmental Hygiene II*, Eds. NH Seemayer and W Hadnagy, Springer Verlag, Berlin, pp. 7-10 (1990)).

Hathaway

Comment: "It should also be mentioned that particle overload is a non-specific tumorigenic mechanism seen in rats and not in other animal species. It may not be relevant to humans."

Response: The text was modified to reflect more current thinking and results.

Epidemiologic evidence

Cole/Corn/Mandel

Comment: "Reference should be made to a short follow-up period, not to a short 'latent' period. The term 'latent' is prejudicial as it implies that there is an effect." (Page 7, para. 3)

Response: We agree that "short follow-up period" is more appropriate and have made changes to comply with this.

Summary of published studies

Cole/Corn/Mandel

Comment: "Several studies are commented upon as being of 'low power.' But, low power, or precision is an irrelevant criticism to offer of a series of studies unless they are collectively imprecise. It seems clear from table 2.1 that the follow-up (cohort) studies are negative." (Page 8, table)

Cole/Corn/Mandel

Comment: "The results of the case-control studies are mixed to slightly positive. A discussion of some of the weaknesses of these studies and a detailed effort to reconcile the follow-up and the case-control studies would be helpful." (Page 11, table)

Howard, MSHA

Comment: "Despite problems involving insufficient latency, exposure uncertainties, and lack of statistical power to detect excess risk, 14 of the 18 cohort studies indicated some excess risk. We suggest that you point out that although weaknesses in the studies make it difficult to draw reliable quantitative conclusions, taken together they seem to qualitatively demonstrate a positive association." (Section 2.C.1)

Response: These opinions are evidently contradictory. We feel that no change is necessary. With regard to including more material and debate on the pros and cons of the different studies, we disagree. The protocol is not intended to be a detailed review of the scientific literature, nor a debate on the relative

merits of different studies and approaches. Such documents already exist. We do agree, however to change the words "low power" to "small study" as appropriate. That terminology is more specific and appropriate.

Summary of epidemiology

Howard, MSHA — Comment: "Weak evidence of excess risk should not be confused with a weak or 'moderate' increase in risk. Although an epidemiological estimate of relative risk equal to 1.5 may constitute weak evidence, a fifty-percent increase in risk is substantial, if it actually exists."

Response: We concur with this point.

SECTION 3 - FEASIBILITY STUDY

Cole/Corn/Mandel — Comment: "... More information should be provided on the criteria and the methods to establish the adequacy and completeness of the records."

Response: Appendix B has been revised to describe better the criteria and procedures used in the selection of mines..

Cole/Corn/Mandel — Comment: "...The possibility that the one mine sampled is atypical should be ruled out."

Response: From examination of prior data for the sampled mine it does appear that it was fairly typical. To some extent it is not important that the mine be very typical of other mines. The main point of the study was to examine the correlation between assessments of diesel exhaust using elemental carbon and other state-of-the-art techniques and older measures, such as NO_2. For this to be done adequately, there is no need for the mine to be typical.

Cole/Corn/Mandel — Comment: "Because radon is such a potent lung carcinogen, it should be confirmed that the low levels prevail throughout the selected mines."

Response: On p. 29 of the existing protocol we say that, "Sampling for radon will be conducted one time at each area sampling location to confirm the reported low levels of radon exposure."

SECTION 4 - STUDY OBJECTIVES

Cole/Corn/Mandel — Comment: "Objective I) implies that causes of death other than lung cancer will be evaluated, yet no rationale for this is provided."

Response: Although we feel that the main emphasis should lie with lung cancer, it would not be prudent nor ethical to ignore non-lung-cancer information pertaining to mortality status in the cohort study. In this, the scientific literature has shown evidence of excess mortality from certain other causes. These will be treated as *a priori* hypotheses. Finally, *a posteriori*

elevated death rates for other causes will be investigated in the context of hypothesis generation. The case-control study will examine only lung cancer. If other causes of death appear worthy of further study, separate protocols will be considered for this purpose.

Cole/Corn/Mandel — Comment: "What other 'potential confounders' will be included in the mortality analyses and how will these be ascertained."

Response: These topics are dealt with fully in Sections 5 and 6.

Seixas — Comment: In reference to stated study objectives (hypotheses), "There is no clear distinction made between hypotheses I) and ii) on page 13 and as restated in the introduction to the case-control study on page 19. They both indicate testing the hypothesis of an exposure-related increase in lung cancer."

Response: This is a valid point, and the hypotheses have been modified.

Schenker — Comment: "The study objectives do not at all clarify how this study (biomarker) will address the primary investigative hypothesis."

Kerr McGee — Comment: "It is therefore crucial that the study protocol is carefully designed to assure that; ... all proposed mechanisms of carcinogenesis are evaluated ..."

Response: See Biomarker section responses.

SECTION 5 - COHORT STUDY

Gibbs — Comment: "The study protocol should be modified to take advantage of any pre-dieselization data available..... A pre- and post-dieselization study would control for all confounders except time period."

Response: We do not think it is feasible to make this change, since many of the study mines started operation the same year as, or very shortly before, dieselization, as shown in the table below.

MINE #	COMMODITY	FIRST ACTIVE	YEAR OF DIESELIZATION
Primary Mines			
6	TRONA	1967	1967
7	TRONA	1962	1962
8	TRONA	1949	1965
13	SALT	1959	1960
15	LIMESTONE	?	1960
16	POTASH	1964	1964
18	POTASH	1952	1952
19	POTASH	1964	1964
21	POTASH	1940	1950
23	SALT	1898	1962
Back-up Mines			
2	LIMESTONE	1947	1948
12	SALT	1962	1963
17	POTASH	1930	1950
24	SALT	1948	1950

Causes of death to be analyzed

Shy

Comment: "In the analysis plan for the cohort study, no mention is made of cause-specific analyses other than lung cancer. Are there any *a priori* expectations regarding cardiovascular and non-malignant respiratory disease associations with diesel exhaust?"

Schenker

Comment: "The specific diseases other than lung cancer should be specified before the analysis."

Response: The outcome of primary interest is lung cancer, but there are *a priori* expectations for some other diseases to be associated with diesel exhaust exposure. In the summary of the 1989 IARC monograph on diesel and gasoline exhausts, (IARC, 1989) bladder cancer, multiple myeloma and lymphoid leukemia were discussed as showing elevations in workers exposed to diesel exhaust or mixed engine exhaust. Furthermore, elevations in mortality associated with diesel exposure have been reported for Hodgkin's disease, lymphoid leukemia and several non-cancer outcomes (e.g., cerebrovascular disease, arteriosclerosis, pneumonia and influenza, cirrhosis of the liver (Boffetta et al., Am J Ind Med; 14:403-405), emphysema (Howe et al, J Natl Cancer Inst; 70:1015-1017, Wong et al, Br J Ind Med: 42:435-448) and

chronic respiratory disease (Garshick et al., Am Rev Resp Dis; 135:1242-1248)). As suggested by Breslow and Day (Breslow and Day, *Statistical models for cancer research*, IARC, 1987) in the chapter on the role of cohort studies, results from *a priori* stated outcomes will be given more weight, while the results for other diseases will be treated as hypothesis generating. The protocol was changed accordingly.

Criteria for inclusion in the study cohorts

Cole/Corn/Mandel

Comment: "Why does the intake period stop at 1979. The cost of extending intake to say 1989, would be modest and these more recent workers may prove to be of value." (Page 14.)

Shy

Comment: "It is tempting, however, to want to record data for workers hired after 1979 with a view to future follow-up studies of these same mines, without including those workers in the current study."

Response: We agree that the intake period should be extended. The cohort will be comprised of underground and surface workers who have been employed in the candidate non-metal mines for at least one year during the period between the date of dieselization of each mine and December 31, 1996. A selection criterion of one year of employment during diesel use in the mines will be applied to ensure a reasonable minimum period of exposure. Most surface workers are essentially not occupationally exposed to diesel exhaust. Therefore, the cohort study will include a wide range of exposure to diesel exhaust. The study cohort will be followed for vital status through December 31, 1996. The intake period of the entire cohort was allowed to extend to the end of the follow-up period for three reasons. First, although lung cancer is the disease of primary interest, as discussed above, other diseases, with shorter latent periods are also of interest. Second, further follow-up of this cohort may occur in the future, and third, we need to document the work-histories of all workers in order to fully document exposures of those workers who either moved from mine to mine or were employed at different periods in the same mines.

In the data analysis for specific diseases where the latent periods are known from previous studies, sub-cohorts will be created by cut off at the appropriate date. For example for lung cancer, the diesease of primary interest, where the latent period is about 15 to 20 years, the cutoff date will be set at the end of 1979. Since the earliest date of dieselization of any of the proposed study mines was 1950 and the cutoff date is the end of 1979, the time form first exposure to end of follow-up will range from 16 to 45 years.

O'Toole

Comment: "However, it would be beneficial to examine those employees that are employed greater than one year but less than 5. There are other studies that suggest a short term worker effect may bias results away from the null."

Response: The point is well taken that short-term workers may have other risk

factors for lung cancer. But one could also say that short-term workers may have had the most highly exposed jobs. In fact it is possible that unpleasant working conditions, such as those with high exposure to diesel exhaust, may have caused the workers to remain only for short periods. To explore this effect, we can do the overall analyses with and without those workers. We can also look for increased disease in this group in breakdown by tenure and exposure intensity.

O'Toole

Comment: "Including miners from before 1970 is also troublesome. Available information such as smoking history and/or other relevant lifestyle factors will likely be unattainable. For that reason, inclusion of that group will introduce significant information bias. We would recommend that the study period be from 1970 to 1990. That range will still provide for a latency period that ranges from 20-45 years."

Response: It is not clear what is meant by a study period from 1970-1990. One interpretation is that we only include miners who started work after 1970. This starting date provides for a maximum time from first exposure of 26 years, with an average of about 13 years (rather than the 20-45 years stated above). This is considerably less than that proposed in the protocol. The workers excluded from the cohort by the suggested strategy would have the longest time from first exposure to end of follow-up in 1996, and thus be at higher risk of death from diseases with longer latent periods, such as lung cancer. Hence, the study would be considerably weakened by this approach. In order to compensate for this, its size would have to be substantially increased by the inclusion of more mines, at further expense and inconvenience to all concerned.

Howard

Comment: "Since many workers included in the cohort are expected not to be occupationally exposed to diesel exhaust, the minimum period of exposure is zero. It would be helpful to explain why it is important to include workers with little or no occupational exposure in the cohort."

Response: The unexposed workers are included to allow for analyses comparing exposed and unexposed workers. Use of an internal reference group can solve problems of confounding encountered with the use of external reference populations. Dr. Marc Shenker feels that a good internal comparison reference standard should be the primary comparison population.

Mine Selection

Cole/Corn/Mandel

Comment: "What criteria will be used to determine the "quality" of the records? What, if any, steps will be taken if the records are deemed to be of low quality? How might this affect the study?"

Response: Determining the quality of personnel records was part of the function of the feasibility study. During the feasibility study, site visits were made to estimate the total number of personnel files kept by the mine and to

microfilm a random sample of between 10 to 15 percent sample of the personnel files. Results from the feasibility study samples of personnel records showed that for the 14 mines selected, the worker's name was on 100% of the records, the social security number was on 96% to 100% of the records and the date of birth was on 98% to 100% of the records sampled. Department and job titles, dates of job changes, work-history prior to the mine, (from employment application forms), and names of next-of-kin were available from the personnel records of all the 14 mines. Only those mines with what appeared satisfactory records were retained in the study. After the main record collection phase, poor quality records will be deleted. Poor quality records consist of those with missing identification (e.g., name, SSN, etc), or with missing or inadequate work history. Although deletion is expected to be random, and thus will not cause bias, analyses will in any case be undertaken to check on patterns that might suggest non-random groups of poor or missing data. In this event, a decision on appropriate action will be taken at that time.

Information on smoking

Cole/Corn/Mandel

Comment: "What smoking information would they expect to find in the personnel record? How complete will it be? What do they propose to do with it? It is unlikely that standardized data will be available on smoking practices at the time the records were created and it is unlikely that smoking histories will be uniformly available."

Schenker

Comment: Concern was expressed about taking smoking information from personnel records. He thought that the 1976 NIOSH/MSHA study smoking information the most useful. "What percent of the cohort is expected to have smoking information from the 1976 survey?"

Gibbs

Comment: Expressed concerns about smoking information available from personnel files.

Response: First, smoking is only a concern if it is confounded with the exposure of concern. In occupational studies, as noted by Shy (review of this study), "there is ample evidence that smoking does not confound well designed cohort studies of lung cancer risk." Even if there is evidence of potential confounding, steps can be taken to control for this in the cohort study. For adjustment using the commonly-employed Axelson method in the cohort study, we will employ data from the 1976 NIOSH/MSHA morbidity study enhanced with information gleaned from personnel files. With regard to the percentage of the cohort with smoking information, there is smoking informtion for 70% of the mines (seven of the ten mines had smoking data ascertained during the 1976 morbidity survey). In addition, from an analysis of the personnel file sample taken during the feasibility study, some smoking information was found in the files on 7 of the 10 primary mines and two of the four back-up mines. For estimates of the U.S. population smoking habits during a period towards the earlier part of the study period there are Health Interview Survey data collected by the National Center for Health Statistics in

1965, 1966, and 1970, 1974, and 1978.

Offsite records

Shy

Comment: "Will these records add to the study population of 8200 workers? Will an effort be made to retrieve and incorporate these records if they fit the inclusion criteria?" (Page 15)

Response: Three of the ten mines have personnel records at offsite locations. Visits will be made to the offsite locations to microfilm these records. The number of offsite records is not known.

Data abstraction

Cole/Corn/Mandel

Comment: "This suggests that they will obtain work histories prior to employment in the study mines. They should explain why and how they propose to do this. How complete are prior job histories? What will be done for past mine employment, particularly in view of the high turnover rates in the mines?"

Response: Pre-employment questionnaires on job application forms will be used to obtain work histories prior to employment in the mines. For those individuals who had worked in more than one of the study mines we will use records from all mines to compile the work history. It was determined from the feasibility study, that all the study mines had job applications in the personnel folders.

Gibbs

Comment: "...an occupational history after leaving the study mine's employment is critical....."

Response: It is true for all retrospective cohort studies that there are gaps in the work-history information after workers leave the study mines or plants. For any study, the extent of the missing information will vary among the cohort members and can only be ascertained once the cohort is assembled. Workers who retired from the study mines during the course of the study will have no gaps. Miners who moved between the study mines may also have no or small gaps. We will be able to determine later employment patterns for some workers by matching the records with extensive NIOSH databases of coal miners and other workers.

Cole/Corn/Mandel

Comment: In reference to top of p.16, "Double extraction of all the records may be unnecessary. A sampling strategy for validation would be less expensive."

Shy

Comment: Asks if we should early on assess the need for double abstracting - to save time.

Response: We understand that double abstraction is more expensive. During

the abstraction of the feasibility study record samples, the project officer decided that the error rate was high enough to justify double abstraction. We had budgeted for it and would rather do double abstraction to be sure of the accuracy of our data sets.

Determination of cohort eligibility

Cole/Corn/Mandel — Comment: "How will the completeness of the cohort be determined if Social Security Administration records are not available"

Shy — Comment: "What will be done if the SSA quarterly earnings reports reveals a number of personnel not identified in the basic cohort enumeration? Is this effort worth the time and cost."

Response: We will question the mine administration to see if some personnel files had been missed during the visit, and retrieve these records. If the records cannot be obtained, we will at least know the extent of missing records. Some missing data can be tolerated, since there may be little actual bias introduced in an assessment of cause-specific mortality by including mines with missing data(Steenland et al., Am J Ind Med; 12:419-430). We will also try to collect payroll records and seniority lists for the time-span of the study from the company and/or the unions. We will use these lists to make a systematic computerized check of the completeness of the personnel records.

Follow-up procedures

Cole/Corn/Mandel — Comment: "...some comment should be given to the likelihood of complete ascertainment in the early years (particularly the 1950s-through 1970s) of follow-up."

Response: For each study mine, the start of follow-up is, at the earliest, one year after the date of dieselization. The dates of dieselization in the primary mines are shown in the table given near to the start of this section. Of these ten mines, only two began using diesel in the early 1950s, while the other mines began in the early to mid 1960s. Thus only a small portion of the cohort may have died during the 1950s. For the death from the 1950's to 1979 we may indeed have trouble in achieving a 100% vital status follow-up, if we relied on SSA Death Master File information alone, (as is discussed below), which we do not. The manual for the CSRA Inc. Nationwide death Index CDS compiled from the SSA death tapes claims that from 1962 to the present about 76% of all decedents are recorded on the data base. Among those omitted, the majority died relatively young and were therefore less likely to have much to do with the social security system. CSRA states that the probability of finding someone who died after age 60 after 1962 is better than 80%, while the chance of finding someone who died in their twenties is 40%-50%. In many cases the reason for a no-hit lies not in the absence of the record but in the lack of precise information for retrieval, so one can improve the chances of finding a person by trying various combinations of spelling of the name. For deaths

occurring in 1979 or later the National Death Index is between 93-98% effective at identifying known decedents. As stated in Section 5.C.6, iii)and iv), pg. 17. We will use a number of different sources on the study cohort members still considered alive after SSA and NDI, including contact of family members.

Mine-specific analysis

Gibbs

Comment: "Analyse the cohort data by mine....."

Response: Mortality data will be also be analyzed for individual mines as was done by Ward et.al. in a mortality study of workers at beryllium processing plants (Ward et al., Am J Ind Med; 22:885-904).

Indices of exposure to diesel exhaust

Cole/Corn/Mandel

Comment: "What is meant by "lagged" estimates and how does this relate to "latent period"?

Response: Lagged estimates of exposure will be explored. The method assigns an exposure achieved some chosen number of years earlier (the lag period) to a person's current person-year at risk (Checkoway et al., *Research Methods in Occupational Epidemiology*, Oxford,1989). Several different lag periods can be chosen for investigation. It is an attempt to differentiate between the exposure received between the time of first exposure and disease induction, and the exposure received after disease induction but before the case or death is identified, this latter exposure not being relevant to the analysis.

Hathaway

Comment: He thought that only cumulative, as compared to average and maximum exposures should be used, because use of these other indices would cause artifacts for short-term employees.

Response: Since the mechanisms of carcinogenesis are not fully understood, it is prudent to include indices of exposure having a biologic or epidemiologic basis, such as average and maximum exposures, as well as cumulative exposure. Analysis using these indices can be done with and without the short-term workers to see if the results differ substantially.

Cole/Corn/Mandel

Comment: They discuss factors that will lead to inaccuracies in exposure assessment for individual workers, and say all that the potential errors will be compounded. "This aspect of the reliability of the exposure estimation is not addressed in the proposal."

Response: The variability inherent in estimation of worker exposures is a recurring problem in epidemiologic research. Yet, despite this, studies have consistently been able to demonstrate exposure-response relationships. There is no reason to believe that this study should be worse, and good reasons to believe that it will be better in this respect.

Confounding from other exposures

Cole/Corn/Mandel — Comment: Question in regards to the levels of radon, silica and arsenic, and what criteria we will use to determine the levels are below that which might be expected to cause confounding. "What is meant by "unforseen elevations" and how will the investigators determine if confounding "appears to be a problem."

Gibbs — Comment: "Determine expected excess lung cancer risk in the cohort population due to silica and radon based on prior NIOSH or EPA risk assessments and the average exposure levels in the study mines."

Response: The mines selected for study have been documented as having low levels of exposure to radon, silica, arsenic, and asbestos, and thus confounding by these exposures is extremely unlikely to be a problem. However, to be sure, we will measure these substances during the IH surveys and examine the data for elevations and for correlation of the measurements with the exposures of interest. If deemed desirable, analyses will be undertaken with and without controling for these variables in the statistical models, in order to assess any effect of these confounders.

Cole/Corn/Mandel — Comment: Relates to first sentence top of pg.18. "How will employment in other jobs with diesel exposure be taken into account?"

Schenker — Comment: "How will information on "previous employment in high-risk occupations" be obtained? How will it be used in the analysis?

Response: Information for previous employment in high-risk occupations will come from the prior work histories in job application forms. The information will be extracted from the forms and coded for industry and occupation. This information can be used to code workers for work in, for example, uranium mines, and can be included as a variable in the statistical models.

Cole/Corn/Mandel — Comment: They questioned the possibility of confounding by socioeconomic status..."particularly in view of the inclusion of administrative workers who are likely to constitute the baseline ("non-exposed") group."

Schenker — Comment: He was concerned that the administrative staff could be different in many ways from the underground miners e.g. SES. Explore the issues and select an optimal internal control group.

Hathaway — Comment: He was concerned about the inclusion of administrative workers.

Response: We have decided to exclude the adminstrative workers from the cohort due to the concerns expressed about the effect of socio-economic status differences between the administrative workers and other mine workers. The surface workers comprise the main group of non-exposed workers. Thus the exclusion of the administrative workers will not greatly effect the size of the internal reference group.

Hathaway

Comment: "Could the Axelson technique..be described?" "Has this technique been validated?"

Response: The Axelson technique as an application for adjustment for a cohort study, is well described by Steenland and Beaumont (Am J Ind Med, 1989;16:347-354). It is well accepted by epidemiologists as an indirect method of adjustment for confounding.

SMR analysis

Shy

Comment: "For comparison purposes, can a third referent group be considered, namely, the NCI/NIOSH occupational cohorts pooled from previous studies?"

Response: This change has already been made to the protocol, and this referent group included (with the proviso that follow-up for this group has by then been extended to cover the period of the diesel study).

Hathaway

Comment: "What is the Occupational Referent Population?"

Redmond

Comment: More detail was requested on the NCI/NIOSH Computerized Occupational Reference population. She requested a discussion of adapted statistical techniques when utilizing this population and also small reference populations.

Response: The NCI/NIOSH Computerized Occupational Referent Population System (CORPS) is an SMR data base which is comprised of 96,467 workers from 25 NIOSH/NCI studies reflecting 1,947,726 person-years. The CORPS system can generate mortality rates stratified by sex, race, time, age. Subsets of geoghraphic regions and blue collar/whitecollar may be made. Employment duration and employment status (active or terminated) can also be varied. Consideration will be given to applying empirical Bayes methods to stabilize the mortality rates.

Schenker

Comment: "How will an external comparison be used? Will this add anything to the internal comparison population? If multiple external reference populations are used.....which is the primary population. My bias is that a good internal reference standard should be the primary comparison."

Gibbs

Comment: "...should pre-determine which reference population.will be considered primary with regard to final interpretation of the Cohort Study"

Response: The purposes of the cohort study are to identify causes of death that are elevated in the diesel exhaust exposed cohort in comparison to both the internal nonexposed cohort as well as external standard populations, and to run trend analyses with regard to extent of diesel exhaust exposure. The internal nonexposed group will be the primary comparison population. Standardized mortality ratio analyses using external reference populations are a standard method of cohort analysis and will be run to allow comparison of results both

with those of the internal reference group and with those of other cohort mortality studies.

Redmond

Comment: Concern was expressed about analytic issues associated with the use of smaller external references populations with regard to stability of rates.

Response: We will use the U.S. population and State populations as the external reference groups . County populations will not be used due the instability of the death rates.

Gibbs

Comment: He would like the reference population adjusted for smoking status, blue collar/white collar status, mining occupation, and would like to know how endpoints are established.

Response: Use of the internal reference group as the primary reference group will address these concerns. For U.S. reference populaton comparisons we will adjust SMR's for smoking using the Alexson indirect adjustment as described in the protocol. Death certificates are used for all the reference population death rates.

Regression analysis

Cole/Corn/Mandel

Comment: "In the regression analysis, it is proposed to include in the model information on asbestos, radon, arsenic and silica if necessary. The investigators should explain what they mean by "if necessary".

Response: See the response noted above in the sub-section entitled *Confounding of other exposures.*

Cole/Corn/Mandel

Comment: "Explain the use of "biologically-based mathematical models."

Hathaway

Comment: Asked what biologically-based models means.

Response: Biologically-based mathematical models of carcinogenesis are models which incorporate biological theories of the mechanisms of carcinogenesis. In the multistage theory, a cell progresses through a series of ordered and irreversible stages. The multistage model provides information on whether more than one stage is exposure-related, and assists in determining at what stage the carcinogen acts. Moolgavar and colleagues have developed a two-stage model that allows for the influence of exposures on cell growth and differentiation as well as on the first mutational event that results in an intermediate cell and the second mutational event that completes the transformation to a malignant cell (Mazumdar et al., 1991;90:270-277) Stayner et al. applied amongst other models, both multistage and two-stage biologic models to a study of lung cancer among workers exposed to cadmium to illustrate the modeling methods (Stayner et al., Am J Ind Med, 1995;27:155-170). For the diesel study data we will supplement the conventional analysis with these modeling techniques.

Shy

Comment: Cautioned about entering interaction terms into the models. "...thus interaction terms should be modeled with due conservatism." (Page 18)

Response: We agree. The protocol now reads that interaction terms will be entered only if biologically plausible and even then with conservatism due to the ensuing lack of power.

Power calculations

Schenker

Comment: "A RR of 1.5 should be used in the calculations."

Response: This is now included in the protocol

Howard

Comment: "How sensitive are the power calculations to the distributions of the cohort's duration of exposure, age and latency period?"

Response: We expect 120 lung cancer deaths in the full cohort under the null hypothesis of no effect of diesel exposure for an estimated 184,189 person years of follow-up, based on the data obtained from the 10-15% samples of personnnel records taken from the mines during the feasibility study. The power calculation is based on actual data, and consists of far more information directly pertinent to the cohort than is usually available for most proposed studies. In view of the number of records sampled this estimate is believed to be reliable, and sensitivity is not a major concern. The actual cohort size is expected to be somewhat larger than 8200, due to offsite records not accessed during the feasibility study (no estimate of how much larger can be made at this time), thereby increasing the power still further.

Hathaway

Comment: "It would enhance the protocol if power calculations were added for a negative study. For example what is the power to detect an SMR of 1.1.

Response: The concept of power of a study relates to the probablility of finding an effect if it truly exists. The power of a negative study is therefore a meaningless concept. However, power calculations for a small effect such as an SMR of 1.1 can be done. For this cohort with 50% exposed, 60 lung cancer deaths are expected under the null. An SMR of 1.1 gives 66 deaths, with power of the order of 15%.

SECTION 6 - THE NESTED CASE-CONTROL STUDY

Potential confounders

O'Toole

Comment: "The proposed case-control study will fail to provide useful information if tobacco smoking is not adequately documented for both cases and controls." "Identifying and coding a cases' or control's prior work history, as well as work history since leaving the mine could be vitally important."

Response: To the data collection section (section 6.C.1), a list of all smoking-

related questions has been added. As indicated in the original protocol (see page 20), a history of lifetime employment in occupations at high risk for lung cancer will be obtained. These data will be treated as potential confounders in the analysis.

Schenker

Comment: "I would suggest that the primary and major goal of the next-of-kin study should be obtaining a smoking history, for which there are existing data on feasibility and validity. How will smoking data from other sources be used?"

Cole/Corn/ Mandel

Comment: "...it is not obvious that supplementing interview derived data on smoking with data from other sources is appropriate. Care must be taken to achieve similar ascertainment of all information from the cases and controls to ensure valid comparisons."

Response: The primary purpose of the next-of-kin interview is to obtain information on smoking. We also plan to supplement the interview data with smoking data obtained from the 1976 cross-sectional survey and from company medical records. Information on smoking will be ascertained in the same way for cases and controls. Smoking data from all sources will be used to control for confounding in the analysis.

Woskie

Comment: "Given the high levels of diesel exhaust in some urban areas, will information on where the subject has lived be collected? Farm equipment and personal light duty diesel trucks and cars are also potential diesel exposure sources."

Response: Although a lifetime residential history is time consuming and is probably beyond the limits of a next-of-kin interview, we will add a few questions regarding urban vs. rural residences (see section 6.C.1). Use of other diesel equipment was already included in the questionnaire.

Response rates

Cole/Corn/Mandel

Comment: "Cohort members may have died of lung cancer as many as 40 years ago. Thus, contact with their next of kin is problematic, and even for those contacted, there will be question about the reliability of the data. It would seem highly desirable to limit the case-control study to recent diagnoses of lung cancer. Systematic loss of early cases is acceptable, and may be of minor concern since an effect of diesel exposure may only occur after several years from first exposure."

Schenker

Comment: "The next of kin response rates again appear optimistic, given the amount of time possible since death. Is this estimate based on a comparable study in another population?"

Response: The systematic loss of early cases is unacceptable because we would be eliminating those cases with the longest time from first exposure to

end of follow-up. While an effect may occur after only a few years from first exposure, it is more likely to occur after a longer time interval for most solid tumors including lung cancer.

We, too, are concerned with locating next of kin of individuals who died on average 25 years ago. Data from a previous NCI nested case-control study of lung cancer among pest control workers employed in 1965-69 indicated that 95% of the surrogate respondents were locatable and 83% were actually interviewed (Pesatori et al., Cancer Causes and Control 1994;5:310-318). Our goal of achieving a 75% response rate from the next-of-kin interview seems reasonable. The plan to supplement the smoking data with information from other sources is intended to minimize the number of subjects with missing smoking histories due to nonresponse from the next-of-kin interview.

Lung cancer as a contributing cause of death

Hathaway
Cole/Corn/Mandel

Comment: "There is no objection to using decedents with lung cancer as a "contributing cause". However, there will be few, or no such persons. The words "due to" are inappropriate if a contributing cause is referred to."

Response: We agree. Section 6.B.1 has been changed to read "Cases from each mine will be all lung cancer deaths (ICD-O = 162) as specified ..."

Interviews on next-of-kin

Seixas

Comment: "Conducting interviews on surviving controls while all other interviews are with next of kin suggests a potentially important source of information bias. This is particularly important since an attempt will be made to blind interviewers from case status. I would think that next of kin interviews should be used exclusively."

Hathaway

Comment: "Will the fact that many, if not most controls will have a direct interview versus next-of-kin interviews for cases result in significant variations in accuracy of responses? Could some next-of-kin interviews be performed on living controls to compare responses between subjects and next of kin? It seems to us that there will be little blinding since most controls will be living and most of the deceased will probably be cases."

Response: The interview in this study is designed primarily to obtain information on confounders. In this situation, there is no literature to support the notion that matching on type of interview will result in comparability of information from cases and controls (Walker et al., Am J Epidemiol 1988;127:905-914; Wacholder et al., Am J Epidemol 1992;135:1029-1041; Wacholder, personal communication). In fact, conducting an inteview with the next of kin of a living subject is not comparable to conducting an interview with the next of kin of dead subject. Taking all factors into account, we feel it is preferable to obtain the most accurate information possible for both cases

and controls.

Redmond — Comment: "The statement that efforts will be made to "blind the interviewers with respect to case/control status" does not seem reasonable in a study where the information on cases will come from next of kin, whereas controls will usually be providing information on themselves."

Cole/Corn/Mandel — Comment: "How will the study be blinded from the interviewers? What about the respondents? What will they be told regarding the purpose of the study?"

Hathaway — Comment: "Hopefully interviewers will be blind to the status as diesel particulate exposed or not. Any questions that might reveal this status should be asked at the end of the interview."

Response: Interviewers will not be told that all the cases are deceased so they will not know that all direct interview are with controls. Neither the interviewers nor the respondents will be told the case/control status. Subjects will be told that the purpose of the study is to learn about how environmental factors, such as smoking, affect health. The following has been added to section 6.C.2: "Every effort will be made to blind the interviewers with regard to case/control status and diesel exhaust exposure. Interviewers will not be informed that all cases are dead and some controls are living. Thus, they will be unable to surmise that if an interview is conducted directly with a respondent, it must be that of a control."

Cole/Corn/Mandel — Comment: "All the cases will be deceased and some will have died many years ago. It is likely that many spouses and siblings may also be deceased. The investigators should provide justification for relying on "close relatives" or "children" for historical information, particularly in view of the fact that many, and perhaps most, controls will be interviewed directly."

Response: This cohort is relatively young. The average age in 1995 was 54 years old. Thus, we are expecting that most of the spouses (almost entirely wives in this study) will be alive at the time of the interview.

Use of telephone interviews

Cole/Corn/Mandel — Comment: "The investigators should justify the use of telephone interviews given the magnitude and cost of the study."

Response: The determining factor in the decision not to conduct in-person interviews in this study was the length of the interview. Because the primary purpose of the next-of-kin interview is to obtain information on potential confounders, the interview will be relatively short. The added expense of conducting in-person interviews in this study seems unwarranted.

Pathology slide analysis

Schenker

Comment: "What is the purpose of the pathology slide analysis? Will cases not-confirmed by pathology be changed in the analysis? If cell type is analyzed how will it be used in the study? What about mixed cell types? How feasible is it to obtain pathology slides on a reasonable percentage of lung cancer cases? This looks like a fishing-expedition with no clear aim, nor value to the investigation. I think that the pathology analysis is of dubious feasibility and value. My suggestion would be to conduct a small feasibility study of how many pathology specimens can be obtained. The specific aims of the pathology analysis should also be spelled-out."

Hathaway

Comment: "The protocol should clarify whether pathology reviews will be used to exclude cases that are not lung cancer."

Response: The following has been added to section 6.B.1: "The purpose of the slide review is to confirm the diagnosis of lung cancer as well as the histologic subtype. For cases with no slides, pathology reports will be considered acceptable confirmation of diagnosis. Cases that are found either not likely to be carcinoma of the lung or metastatic to the lung by slide review or pathology report will be excluded from the analysis. Cases with no slides or pathology report (i.e., clinically diagnosed cases) will be included in the analysis. If the proportion of cases with usable slides is high, histologic subtype-specific analyses will be considered."

Selection of controls

Gibbs

Comment: "Control selection should take into account: 1) regular use of respirators, whether or not use was mandated; 2) exposure to any other non-absorbable dust in the submicron range; 3) employment above ground or underground."

Response: The rationale for taking these factors into account in control selection is unclear.

Shy

Comment: "Is matching of controls on mine essential, considering the possibility of overmatching cases and controls on exposure environments? Another option is to pool workers into three or four geographical units and match cases to controls on these broad geogaphical units, e.g., New Mexico mines, Wyoming mines, all other mines."

Response: Matching on mine should not lead to overmatching because there is considerable variability in diesel exposure within each mine. Within each mine, diesel exposure varies by location in the mine, job title, and time period. Because the quality of historical exposure data varies by mine, matching on mine is desirable. Moreover, it provides a built-in control for unknown confounding analogous to matching on hospital in a hospital-based, case-control study.

Redmond

Comment: "The intention to match on mine, gender, race, ethnicity, and year

of birth (within five years) with a ratio of four to one may prove difficult. It would be useful if some initial estimation were presented of the anticipated distribution of workers according to the mine, gender, race, ethnicity and age. While the matched plan seems reasonable, it would be worthwhile to explore its feasibility prior to implementation of the case-control study."

Cole/Corn/Mandel

Comment: "Four controls per case is inefficient. It may be preferable to make no commitment to any selection ratio until preliminary results indicate how many cases there will be. Power per subject, and usually power per dollar, are optimized with a selection ratio of one. At 98 percent power, the proposed study may be larger than need be."

Response: We acknowledge that four cases per control is possibly excessive. Accordingly the allocation ratio has been revised to 3:1. When enumeration of the cohort by mine, gender, race/ethnicity, and age is complete, we will evaluate the feasibility of our plan for control selection and revise it if necessary (see section 6.B.2). We disagree, however, that the optimal strategy is 1:1. For the same power, fewer controls per case would mean a need for more cases. This would require further mines to be included in the study, which is considerably more expensive than interviewing more controls from fewer mines.

Information on diet and pesticide use

Redmond

Comment: "With respect to the data collection in the case-control study, since the emphasis is on lung cancer, the justification for collection of information on dietary factors (or how the data will be summarized) was not clear."

Shy

Comment: "I question the addition of questions on dietary factors. This variable is difficult to specify with reasonable accuracy unless you devote an inordinate amount of questionnaire space to it. Imprecision in the measurement of confounders can bias in either direction, and diet has not been shown to be an important confounder in occupational case-control studies, especially when cases and controls are matched on race/ethnicity and occupation. Is there positive evidence for the need to query on diet?"

Schenker

Comment: "Will next of kin be able to give useful information on diet, other employment, medical history, etc, especially if it is not a spouse (and even if it is)?"

Comment: "Why is pesticide exposure being queried, and how valid is this? Obtaining useful pesticide exposure data from a non-farming subject, let alone a next of kin, is extremely difficult. Further, the weight of evidence is that pesticides are not associated with an increased risk of lung cancer."

Response: The main thrust of the next-of-kin interview is to obtain detailed smoking histories. Because we are conducting a next-of-kin interview, it seems prudent to also collect information on other potential confounders (even

minor ones) for which next of kin have been shown to be able to provide reliable information. With regard to diet, only a few basic questions on fruit and vegetable consumption, which has been shown to be protective for lung cancer, will be included in the questionnnaire. Most next of kin in this study will be wives, and wives have been found to provide reasonably good dietary histories for their husbands, particularly for broad categorical data (Samet, Surrogate sources of dietary information, Nutritional Epidemiology, Willett (Ed), 1990).

With regard to pesticide use, next of kin may not provide reliable information and we have decided to eliminate pesticide use from the questionnaire.

Analytical methods

Shy

Comment: "Has consideration been given to the analysis of exposure time-windows?"

Response: Analysis of exposure time-windows has been added to section 6.D.

Case-control studies on other causes of death

Redmond

Comment: "If feasible, expansion of the nested case-control study to include deaths due to non-lung repiratory sites, and possible also deaths due to non-malignant respiratory diseases, might be worthwhile. If there is an association between diesel exhaust exposure and these other causes of death in the cohort study, it will be disappointing not to have the more detailed information that will be collected in the case-control study."

Response: There are a number of *a priori* suspect causes of death in relation to diesel exhaust exposure (i.e., cancers of the urinary bladder, kidney, colon, rectum, multiple myeloma, leukemia, and nonmalignant respiratory disease) . If any of these causes of death is elevated in our cohort and if the number of deaths provides sufficient power, we will consider developing a separate protocol for a case-control study for that cause of death.

Other issues

Redmond

Comment: "The use of the term "keypunched" for data entry seems to be out of date. Most studies would rely upon some form of key entry through a PC. Perhaps this is what the investigators intended."

Response: The term "keypunched" has been replaced with the term "data entry".

Hathaway

Comment: "The protocol should clarify what would occur if the number of cases of lung cancer is equal to or less than the number of expected cases. Would the case-control study be performed?"

Response: Yes. There may be an association between diesel exposure and increased lung cancer mortality without an overall excess of lung cancer deaths in the cohort study.

Hathaway

Comment: "What would be the power to detect odds ratios of 1.0, 1.1, 1.2? If the power is greater than 80% and the results are less than this, then it should be concluded that there was no association."

Response: A power curve has been added to the protocol (see Figure 6.1). The power to detect such low risks is below 50%.

Cole/Corn/Mandel

Comment: "Describe the "special efforts" that will be made for hard-to-locate cases."

Response: For next of kin that prove difficult to locate, we will attempt to find them through such sources as the U.S. Postal Service, Motor Vehicle Registration Offices, and Credit Bureaus.

SECTION 7 - THE BIOMARKER STUDY

Justification for the biomarker component

Schenker

Comment: "I have the most problem with this component of the investigation. The study objectives do not at all clarify how this study will address the primary investigation hypotheses. Will the results of this investigation impact the epidemiologic studies being proposed? The proposal states that if diesel exhaust exposure is associated with lung cancer mortality, the information gained from the biomarker study may help clarify the role of diesel exhaust in carcinogenesis, and supply insights into biologic mechanisms. It is not at all clear how this will be achieved by the biomarker study. The specific aims of the biomarker study should be clarified and spelled out. As written it is a non-essential supplement to the epidemiologic studies. I think that the cohort study provides an important opportunity to do the biomarker study, and that useful information will be obtained from the study, but the specific aims need to be clarified in the proposal. In general, is this a study to investigate mechanisms of effect, to improve estimates of exposure, or both?

Cole/Corn/Mandel

Comment: "The biomarker study appears to be a study in pursuit of an explanation for a problem that is not known to exist. This study should be justified."

Response: The scientific objectives of the biomarker study are to compare nitro-PAH metabolite and DNA adduct levels in workers exposed to diesel exhaust with levels found in unexposed controls. The importance of obtaining insight into the bioavailability and genotoxic potential of potential carcinogens, and the incorporation of this information into the evaluation of the carcinogenic potential of a particular exposure, has been recognized by International Agency for Research on Cancer (IARC) (IARC, 1994; IARCI,

1996). It is becoming standard practice to incorporate such studies into state-of-the-art research in occupational cancer. This has now been explicitly stated in the protocol (7.A). The study's primary goal (i.e., to obtain insight into the bioavailability and genotoxic potential of nitro-PAH from diesel exhaust exposure) and secondary goal (i.e., to enhance exposure assessment for the cohort/case-control study) have been clarified (7. B.). An interpretation of results from the biomarker study in the context of results from the cohort/case-control study has been provided (7. J.1). The feasibility of using the biomarker data to enhance exposure assessment has been discussed (7. J.2).

Nitro-PAHs and carcinogenesis

Schenker

Comment: "How does the focus on nitro-PAHs relate to the introduction that discusses the two current theories for diesel carcinogenesis, particle overload vs. PAH?"

Gibbs

Comment: The introduction (7.A) referenced two potential mechanisms for a hypothesized carcinogenic effect of diesel particulate; however, the biomarker protocol is designed only to look for evidence to support a genotoxic mechanism (and a consequent zero threshold risk assessment model).

A non-genotoxic "lung overload" mechanism has been hypothesized by several authors to explain the carcinogenic effect of diesel, carbon black, titanium dioxide and other submicron particulate dusts observed in recent rat studies. If this mechanism were proven true, it would corroborate rat study data and support a risk assessment model with a no-effect threshold. If not substantiated, it would indicate that the rat studies may be irrelevant with regard to human cancer risk. The lung overload hypothesis could be tested by:

A. Performing a second nested case control study comparing the pathology slides, identified in the first case control study with additional pathology slides identified from other lung cancer victims. Underground mining, diesel exposure, age, sex, smoking and other confounders could be controlled for. Endpoints would be pre-determined based upon review of pathology slides from recent rat studies that appear to show an association between diesel particulate exposure and lung cancer.

B. Adding lung lavage tests to the biomarkers protocol to determine whether or not diesel exposed miners are "lung overloaded". It would be necessary to control for cigarette smoking as well as other submicron particulate.

Response: Review of the recent literature (Mauderly, Lung overload: the dilemma and opportunities for resolution in *Particle overload in the rat lung and lung cancer: implications for human risk assessment*, Washington DC, eds. Taylor and McCunney, 1996; Snipes, Current information on lung overload in nonrodent mammals: contrast with rats in *Particle overload in the rat lung and lung cancer: implications for human risk assessment*, Washington

DC, eds. Taylor and McCunney, 1996) suggests that particle overload in less likely to be relevant for humans (see 7. A). Further, direct evaluation of the presence of particle load in humans involves either giving subjects a radio-labelled tracer to assess particle clearance or conducting pulmonary lavage. Neither of these approaches is warranted at this time given the lower likelihood that this is an important mechanism in humans. Such invasive studies would only be considered under scenario 5 in section 7. J. We previously noted that we would attempt to collect pathologic samples from cases for molecular analyses. If an adequate number of samples can be collected from cases, we had considered collecting samples from a series of lung cancer cases unexposed to diesel exhaust for comparison. We have added this intention to the protocol.

Specificity of DNA adducts

Schenker — Comment: "Are the nitro-PAHs that will be studied a good marker of the risk of cancer from diesel exposure, i.e how specific are the markers to be measured?"

Schenker — Comment: Specific prior hypothesis for food-related changes in measured biomarkers should be spelled out prior to conduct of the study.

Hathaway — Comment:. "How specific to diesel exhaust are nitro-PAH DNA adducts? Same question for l-acetylamino - 6(8) - hydroxypyrene? What type of other exposures might cause these to be elevated? Only cigarette smoking is discussed as a confounding exposure. Could hunting or target practice (nitrobenzene as a gun cleaning solvent, ammunition loading, etc.) be a confounder? Could blasting in the mines be a confounder? What food items or medications could affect results?"

Steenland — Comment: "You should discuss how specific the proposed DNA adducts are expected to be for diesel exhaust."

Response: Although nitro-PAH biomarkers are thought to be reasonably specific for diesel exhaust, this has not been tested in exposed humans. However, stratifying the analysis by smoking status, which impacts on PAH and probably to a lesser extent on nitro-PAH measures, and adjusting for other potential sources of PAH/nitro-PAH exposures (the most likely of which is grilled meat intake), will allow us to take into account these other potential influences. There is little information on whether hunting, target practice or blasting could impact on these measures. Questions on these practices and recent medication use will be asked in the questionnaire and adjusted for in the analysis.

Kinetics of diesel exposure and study design

Schenker — Comment: "Have the kinetics of diesel exposure, and of other sources such as smoking, been considered in the study design and analysis? What about

non-urinary clearance?"

Woskie

Comment: "It would be helpful to have some rationale for the exposure monitoring scheme. In order to match the relevant exposure period with the biomarker measure, it would be helpful to have some background information on the half-life of the exfoliated sputum and urothelial cells, the white blood cells, and the urinary metabolite, as well as the time course for adduct formation, if it is known. Is it clear from the life-span of these target cells that the exposures during the week of biomarker collection are the most relevant exposures? Since urine samples are being taken at the beginning and end of the week, blood during the middle of the week (day 3), and sputum at the end of the week, it would seem that, at a minimum subject exposures should be sampled for the whole week rather than just days 3-5. Given all the effort to collect the biomarker information, it would seem important to collect well timed and adequate exposure information. How will the personal sampling be done?"

Santella

Comment: "Sample Collection: In general the protocol for sample collection seems appropriate. The only question is why the blood sample is to be collected midweek and not on day 5 with one of the sputum samples. It is likely that if adducts accumulate during the work week, higher levels will be observed on day 5 than day 3. Thus, the sensitivity of the study might be increased with a later timepoint sample."

Response: The anticipated kinetics of the primary biomarkers selected for study have been added, and the exposure assessment approach designed to collect information during the appropriate time windows is discussed in 7.D and 7.E. An attempt will be made to collect samples at the end of the work period (which can be as long as 10 days), subject to logistic considerations.

Regarding non-urinary clearance, it is well established that metabolized PAHs are cleared through both the kidneys and the GI tract. Multiple studies have shown that urinary levels of PAH metabolites (i.e., 1-OH-pyrene) correlate with inhaled and ingested sources of PAHs, so it is unlikely that interindividual variation in the partitioning of urinary versus GI clearance of PAHs is so great as to obscure such relationships. One preliminary study has shown a strong correlation between inhaled particulates on the previous days and urinary levels of a nitro-PAH metabolite (cited in 7.A).

Biological samples

Steenland

Comment: "Presumably you mean to include post-shift urine samples in this "objectives" statement as well as morning. p 23, 7B, part (i)."

Response: The purpose of the first pre-shift sample at the beginning of the work-week is to obtain a "clean" baseline sample. We are not collecting a post work-shift sample on that day since it is unlikely that most of any impact that respiratory exposure has on urinary metabolites will be quickly seen.

Schenker

Comment: "On what preliminary data do the investigators expect to get expectorated sputum from nonsmokers? This seems very unrealistic."

Shy

Comment: "I question whether it is worth inducing the sputum samples in order to measure DNA adducts in this source of samples. How likely is it that sputum samples will be adequate to measure DNA adducts? Should this issue first be resolved on a small early sample of the participants before proceeding with sample collection from all subjects? Is there literature evidence that sputum samples give better results than peripheral blood samples? The investigators propose to induce sputum twice from each subject; the procedure is time consuming and somewhat aversive."

Response: There is only a small amount of preliminary data, cited in 7. E and 7. H, supporting the efficacy of collecting noninduced sputum samples from both smokers and nonsmokers. Additional pilot work is being conducted to evaluate the amount of cells obtained for DNA adduct analysis. Further, the analytical methodology is still being refined (7. H). The evaluation of DNA adducts in the target site is an important scientific goal. There is no literature on the correlation between adducts in sputum samples and in white blood cells. In general, however, attempts should be made to obtain cells from the target site where possible and acceptable to study subjects. Further methodologic work will optimize sample collection. If possible, noninduced samples will be collected. Samples will be stored until the analytic methodology is fully developed.

Schenker

Comment: 6. "A blood sample of 125 ml is almost a blood donation. Is this volume necessary?"

Steenland

Comment: "125 ml of blood? That seems like an awful lot. Do you really need that much? Are you planning to pay these people?" (Page 24)

Response: A blood sample donation is about 450 ml. A 125 ml volume is necessary for this study in order to carry out assays currently being planned as well as to bank samples for potential analyses in the future (see revisions to 7.G). Similar amounts of blood have been collected in other studies of the same design. It would be highly inefficient to put into place a complex field study and end up with an inadequate amount of sample. Subjects will be provided with $200 for their participation in the study (7. C)

Santella

Comment: "Postlabeling studies of exfoliated bladder cells are also proposed. A significant proportion of subjects however will not have sufficient sample for this analysis. Talaska reported that sufficient DNA was available from only 40 of 73 subjects (Envir Hlt Persp 99, 289, 1993). We have had similar difficulties in collecting exfoliated bladder cells from males suggesting that 30-50% of subjects will not be assayed. There may be similar problems with the induced sputum samples."

Response: In a separate study, we collected urine samples from each of 48

subjects on two separate days. There was not enough DNA for analysis for about 1/3 of these subjects from the first day's samples. However, there was enough DNA for analysis for all of these subjects after adding in cells collected on the second day (noted in 7. E).

Urine assay

Santella

Comment: "Sample Assays: Urine will be assayed by GC/MS for 1-acetylamino-6(8)-hydroxypyrene as a representative marker of nitro-PAH. No information is given on whether this method has been successfully applied to detection of this metabolite in human samples. An abstract is referred to but no information is given in it on the sensitivity of the method. 1-hydroxypyrene could be used as a backup assay if the method for the nitro derivative is too insensitive."

Response: Although this assay should be sensitive enough to detect 1-acetylamino-6(8)-hydroxypyrene in highly exposed workers, if in fact nitropyrene adsorbed to diesel exhaust particulates is bioavailable, to our knowledge there are no published data on this issue. The measurement of 1-hydroxypyrene in urine has been added to the protocol as suggested.

Phenotyping for acetylation and hydroxylation

Santella

Comment: "The phenotyping for acetylation and hydroxylation capacity by analysis of caffeine metabolites is well established and should present no difficulties. However, enzymes other than NAT2 and P4501A2 may also contribute to activity measured by the phenotyping assay."

Response: As measured by this assay, the NAT2 phenotype is almost perfectly correlated with *NAT2* genotype. Genotyping could be done as a back-up if necessary. There is some controversy over this assay's ability to measure P4501A2, particularly since there is only preliminary evidence of a genetic basis for the observed interindividual variation in humans. A recently developed saliva-based assay may correct for some of the potential problems in the urine based assay. Experts in the field will be consulted before a final decision is made about the best biologic sample to use to measure the caffeine metabolites.

Contribution of smoking and occupation exposure to adduct formation

Santella

Comment: "A question is raised about difficulties in identifying specific adducts in these samples, but it is noted that 'the general level of adducts (both PAH and nitro-PAH) will be of interest. The demonstration of elevated adducts in nonsmoking workers and the determination of the contribution of smoking versus occupational exposure would be a significant contribution to understanding the role of diesel exposure in human risk.'"

Response: We are proposing to quantitate DNA adduct levels in the

mononuclear cell DNA by ^{32}P postlabeling by both butanol extraction and nuclease P1. In general, nitro-PAH, aromatic amines and N-heterocycles are degraded by nuclease P1 and a marked difference in the level of DNA adducts when comparing butanol extraction and nuclease P1 enhancement, would suggest the presence of DNA adducts in one of these classes. Characterization of both diesel exhaust emissions and ambient urban air suggests that aromatic amines are not either present or present at levels below detection. If aromatic amines were present in an oxidizing atmosphere, they would be expected to be readily oxidized. N-heterocycles also do not appear to be present in detectable levels in diesel atmospheres. These compounds are, however, present in tobacco smoke. In the absence of tobacco smoking in the mines, a marked difference between the level of DNA adducts as determined by nuclease P1 and butanol in nonsmoking miners mononuclear cells would be relatively strong, but not definitive, evidence of the presence of nitro-PAH. Although there have been isolated reports of different labeling efficiencies between these two enhancement methods with PAH, these have not been well established and most evidence supports that view that the majority of PAH do not have a different postlabeling efficiency in the two enhancement assays. It is unlikely that these studies will lead to the definitive identification of a specific nitro-PAH DNA adduct. However, the application of relatively new methods in ^{32}P postlabeling followed by HPLC, suggested that tentative identification of such adducts may be possible if they are present at relatively high levels. Galleghar et al. (Environ. Health Perspect., 99:225-228, 1993) demonstrated that unstimulated human lymphocytes exposed for 18 hr to diesel particle extracts exhibited a unique DNA adduct pattern (outside the normal diagonal zone where most PAH are found on TLC) and that this pattern matched several nitro-PAH. Since then several papers have demonstrated by HPLC after postlabeling that specific nitro-PAH and PAH can be tentatively identified by co-chromatography (King et al., Chemical Research in Toxicology 7:503-510, 1994; Moller et al., Carcinogenesis 17: 61-66, 1996).

Potential future studies

Hathaway

Comment: "Since samples are being saved for possible cytogenetic assays, a careful discussion of possible confounding variables should be included. Future analyses should be subject to peer review and input from interested parties." (Section 7 C 5, page 24)

Response: A discussion of potential confounders for cytogenetic and somatic cell mutation assays has been added (7. I). Interested parties will be notified in advance of planned future analyses and invited to provide input.

Participation in the study

Redmond

Comment: "The success of this effort will depend upon the willingness of individuals to volunteer. There is no discussion in the proposal about what problems might be anticipated with the frequency matching; or how many individuals will need to be selected in order to assure an appropriate number

available for analysis. Based on prior experiences what proportion of those selected in the four groups do the investigators anticipate will "volunteer" for the full evaluation?"

Response: Subjects will be provided with $200 for their efforts in this study. Based upon our experience in similar intensive studies, we anticipate a high response rate of eligible subjects. An initial survey of potential mines for diesel exhaust exposure levels will collect data from potential study subjects on matching variables, as well as an initial indication of each individual's willingness to participate in the study (7. C). Based upon both the exposure data and the survey information, an adequate number of mines will be selected to ensure that there are enough subjects for the study.

SECTION 8 - EXPOSURE ASSESSMENT

Zone based approach and associated topics

Seixas
Woskie
Cole/Corn/Mandel
Steenland

Comment: Concern was expressed about the choice of a zone-based assessment approach to the retrospective exposure assessment, rather than job title, or group-based assessment.

Response: The zone-based approach was suggested in the earlier version of the protocol, based on the initial information from the selected sample of work histories from the feasibility mine. When we had detailed information on the work histories, we thought that the mine/department/job title combination approach would be a better approach to capture the between-job variability in exposure levels. The mine/department/job title combination approach is implemented in the revised protocol.

Seixas
Cole/Corn/Mandel

Comment: They noted that details of the method of time-motion pattern assessment study are not presented.

Response: The time-motion assessment study was the essential part of the zone-based exposure assessment approach. Because the retrospective exposure assessment method will be based on mine/department/job title combination, time-motion evaluation study will not be a part of the new exposure assessment method.

Use of area samples

Seixas
Woskie
Cole/Corn/Mandel

Comment: There was concern about the "use of area samples in representing personal exposures," and the "use of historical personal and area samples in the assessment of exposure."

Response: Area samples are not going to be used directly in representing the personal exposure. The area samples of direct surrogates will be collected from each study department and the results will be used in the mine-specific correlation studies. In addition to the correlation studies, both current and historical area samples will be used in estimating exposure levels for each study department defined in the protocol. The results of the both current and historical personal samples will be used in estimating exposure levels for unique mine/department/job title/calendar period combinations.

Exposure variable terminology

Seixas
Woskie
Cole/Corn/Mandel

Comment: Concerns were expressed about some terminology used in the protocol, such as "elemental carbon, rather than diesel particulate," "Homogeneous Exposure Zone," "priority index," and "baseline estimates."

Response: In the new protocol, we have identified three primary direct surrogates (i.e., elemental carbon (EC), submicron particulate (SP), and submicron combustible dust (SCD)) to represent diesel particulate. Elemental carbon was selected as one of the primary surrogates because other surrogates of diesel, such as CO2, CO, NO2, may come from sources other than diesel exhaust (e.g., smoking, welding, and blasting), while elemental carbon primarily originates from diesel emission in the mining environment. We are not using the term "Homogeneous Exposure Zone" in the new protocol, because of the change in the exposure assessment approach. We are also not using the term "priority index" in the new version. The priority of the historical surrogates to be used in the estimation process will be determined by the mine-specific correlation studies. Because we do not have the historical information on primary surrogates, comprehensive correlation studies will be conducted at each study mine. Each historically available surrogate (e.g., NO_2, CO_2, CO, total and respirable dust, amount of diesel used, and amount of diesel equipment used) will be put in a priority order to be used in the assessment procedures based on the magnitude of its correlation with the primary surrogates (i.e., EC, SCD, and SP).

1976 surveys

Howard
Schenker
Woskie

Comment: They requested details of the previous MSHA and NIOSH surveys at study mines: specifically, "What was done during these surveys?"

Response: Details of these surveys are presented in two reports. (1) IH Site report on the feasibility study: A comprehensive IH Evaluation of Diesel Exhaust Exposure at the New Mexico Potash Company's Hobbs Mine, and (2) Summary of the IH data for the Hobbs Mine (results of the MIDAS and MSHA Surveys).

Schenker

Comment: "How does diesel exhaust from underground mining vehicles compared

to exhaust from truck, trains and other above ground vehicles?"

Response: In general, underground jobs have about 5-40 times more exposure than the above ground jobs, depending on the variation of exposure levels by job titles and locations.

Need for pilot study

Woskie

Comment: "It is certainly not uncommon at the start of a such a large study to need to spend some time doing some pilot and/or validation work. It would seem to me that some of this is necessary, with some decision points identified early in the process The protocols for these pilot/validation studies should be included in the overall study protocol."

Response: Before developing the protocol, we conducted a feasibility study at one mine with the following objectives: 1) to test the strategies for the retrospective exposure data collection (e.g., completing the exposure information abstraction forms, communication with safety officers, obtaining mine maps and other exposure related records; 2) to test the strategies for the work history collection (e.g., abstraction and microfilming of the personnel records); 3) to test the comprehensive exposure monitoring program for the current exposure assessment survey (e.g., strategies for the area and personal sampling); and 4) to conduct a pilot study for a mine-specific correlation survey between primary and historical surrogates of diesel exhaust exposure. The results of this effort are presented in a separate report entitled "IH Site Report on the feasibility study: A comprehensive IH Evaluation of Diesel Exhaust Exposure at the New Mexico Potash Company's Hobbs Mine." The results of the feasibility study have provided us with evidence that the same data collection strategies and exposure monitoring program will be effective for the full study.

Definition of exposure indices

Woskie

Comments: "It is stated that a number of exposure indices will be developed. Could they be defined, their calculation described and a biologically plausible explanation given for each?"

Response: We will be using various exposure indices to characterize historical exposures. The major indices include the duration of exposure, intensity of exposure, and cumulative exposure, which are described in the revised protocol. Because we do not know the mechanism of the exposure-response relationship, other exposure indices such as peak exposure, maximum exposure, and longest exposure also will be examined. The results from this will supply insights into the most biologically relevant index.

Collection of case-control exposure information

Woskie

Comments: "It is not clear how the additional information suggested could possibly be collected in a systematic and unbiased way for all subjects in the

nested case-control study. Please describe this approach in more detail."

Response: Exposure assessment in the cohort study will be based on the mine/department/job title combinations, which assumes that everybody in the same combination has the same level of exposure. In the nested case-control study, because the number of subject is manageable, we will attempt to obtain subject-specific exposure information from long term co-workers, supervisors, or safety officers. This will give us additional information to differentiate the variability of exposure between workers within the same mine/department/job title combination. We will develop a special subject-specific historical exposure form to be filled out at each mine/department by the team of department foreman, supervisor, mine safety officer, and long term co-workers. Standard questions, such as the descriptions of the actual jobs worked by the subject, number of diesel-exposed hours per day for those jobs, the specific diesel equipment pertinent to that subjects exposure, and actual use of personal protective equipment will be asked to the team members systematically.

Accuracy of exposures

Gibbs

Comments: "In the event that a lung cancer association is shown with diesel particulate exposure, an accurate historical assessment of exposures will be an essential factor in determining a "safe" exposure limit. Historical exposure assessment must include:
a) a determination of when and if the use of low sulfur fuel was implemented;
b) a determination of when and if the use of diesel exhaust control technology was implemented;
c) the historical use of personal protective equipment (not just whether or not it was mandated)."

Response: The accuracy of the historical exposure estimates is crucial not just in determining a "safe" exposure limit, but also to obtain a scientifically valid exposure-response relationship. We will include the historical information on the use of low sulfur-containing fuel, diesel exhaust control technology and personal protective equipment.

Cole/Corn/Mandel

Comments: "It is very complex to extrapolate today's results from earlier time because diesel engines and fuels are very different today form even five years ago. How will these technological improvements in engines/fuels be incorporated into modeling of emissions? "

Response: We are aware of the fact that technological improvements in engines, fuels, exhaust systems, and control measures have impacts on the level of diesel exposure. We will give a great emphasis to the collection of the historical exposure information on retrospective changes of engine types, fuel type, exhaust type, and control measures at each mine/department combination. Measurement values for the other surrogates before and after the specific change will give us an understanding on the effects of these technological improvements on the diesel exposure levels. We will also have an opportunity to measure the impacts of these

improvements directly in our current IH-surveys using the different type of old and new equipments, high and low sulfur-containing fuels, old and new exhaust and ventilation systems in different study mines. Having both current and historical information on these technological improvements will help us to do more accurate extrapolation from current levels of diesel exposure to historical levels.

Validity of personnel work history records

Steenland

Comments: "Personal interviews for work history might be useful for checking the validity of personnel record-based work histories - since for the most part you will have to rely on company records."

Response: In the nested case-control study we will be collecting full lifetime work histories, including the jobs in cohort periods from each study subject. This will give us a good opportunity for checking the validity of personnel record-based work histories with the personal interview.

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A Summary of Comments and Responses from the Peer Review of the Study Entitled

"A Cohort Mortality Study with a Nested Case-Control Study of Lung Cancer and Diesel Exhaust among Non-metal Miners"

held at the meeting of the NIOSH Board of Scientific Counselors on January 14, 1997 in Washington, DC

April 3, 1997

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LIST OF REVIEWERS

The individuals listed below submitted oral or written comments at or following the Board of Scientific Counselors meeting on January 14, 1997.

Abbreviated Name	Full Name and Source
Chajet	Mr. Henry Chajet, Counsel for the MARG Diesel Coalition
Corn/Cole/Mandel	Two reports by Drs. Philip Cole, Morton Corn, and Jack Mandel.
Davis*	Dr. Letitia Davis, Department of Public Health, The Commonwealth of Massachusetts.
Dement*	Dr. John Dement, Duke University Medical Center
Eisen*	Dr. Ellen Eisen, University of Massachusetts at Lowell
Frank	Dr. Arthur Frank, University of Texas Health Center at Tyler
Frumin*	Dr. Eric Frumin, Department of Occupational Safety and Health, Union of Needletrades, Industrial and Textile Employees (UNITE)
Gibbs	Dr. John Gibbs, Kerr-McGee Corporation.
Hall	Dr. Thomas Hall, University of Oklahoma
Hattis	Dr. Dale Hattis, Marsh Institute, Clark University (review on behalf of the Occupational Safety and Health Administration).
Howard	Mr. Kenneth Howard, Mine Safety and Health Administration.
Landrigan	Dr. Philip Landrigan, The Mount Sinai Medical Center
Moure-Eraso*	Dr. Rafael Moure-Eraso, University of Massachusetts at Lowell
Parkinson	Dr. David Parkinson, Long Island Occupational and Environmental Health Center
Rall*	Dr. David Rall, Director Emeritus of the National Institute for Environmental Health Sciences and the National Toxicology Program.
Sokas	Dr. Rosemary Sokas, The George Washington University
Spear*	Dr. Robert Spear, University of California, Berkeley
Tuggle	Mr. Harry Tuggle, United Steelworkers of America
Weeks	Dr. James Weeks, The George Washington University
Woolston	Ms. DeAnna Woolston, Special Assistant to the President, People for the Ethical Treatment of Animals (PETA)

* Current member of the NIOSH Board of Scientific Counselors.

SUMMARY

The following lists the major modifications we plan to make to the protocol based on the comments received at and following the meeting of the NIOSH Board of Scientific Counselors in Washington, DC on January 14, 1997. In addition to these changes many smaller changes are planned, as described below in the Detailed Comments section (p. 13 et seq.).

Cohort study

Further information will be given on the power of the study. An explanation of the proposed strategy is given in this document.

More information was requested on the criteria for mine selection, and this will be given.

We plan to extend the period during which subjects can be included in the study from 1979 to December 31, 1996.

Clarification on causes of death to be studied will be added.

Case-control study

We plan to reduce the matching ratio to 3:1 from 4:1. Consideration will be given to modifying the matching ratio depending on the eventual number of cases available for analysis.

Further information will be given on the power of the study. A justification of the proposed strategy is given in this document.

Additional material will be added to clarify aspects relating to the pathology slide analysis.

Biomarker study

Further material is being added to justify the inclusion of the biomarker component of the study.

A section will be added to the protocol demonstrating how the biomarker results complement the mortality analysis and providing critical information for their interpretation.

Exposure assessment component

This section is being completely rewritten to reflect a more conventional approach based on standard and often-used job-exposure matrix principles. A justification of the proposed methodology is presented in this document on p.10 et seq.

Reports from the feasibility study will be included as appendices to the protocol.

GENERAL IMPRESSIONS

The following comments were received about the study in general. These are quoted verbatim.

Landrigan

I have read the protocol very carefully. My overall impression is that it is superb.

The protocol is very well written and clearly presented. The literature review is thorough and makes the clear point that previous studies of the relationship between diesel exhaust and lung cancer have not adequately quantified dose.

The proposal for the cohort mortality study is absolutely straightforward and elegant. The study objectives are clearly defined. NIOSH has one of the best units in the United States for the undertaking of cohort mortality studies, and it is a unit whose skills have been proven over the years. I have every expectation that this component of the study will proceed very well.

The nested case-control study will utilize pathologically confirmed cases of lung cancer as the cases and living controls. Four controls will be assigned per case. The methodology is meticulously described. Again, I have every likelihood to believe that this study will be a success.

The biomarker study is an innovative addition to the project. It may or may not add a great deal of science to the overall endeavor, but it is a worthwhile undertaking, and in the context of the overall study I would support it.

Finally, the proposal for exposure assessment is in many ways the crown jewel of this proposal. It builds upon the beautiful work that has been done at NIOSH in past years by such scientists as Rick Waxweiller and Bob Rinsky. It utilizes many of the techniques that Rinsky et al. perfected in their landmark study of benzene and leukemia. The integration of industrial hygiene data to form a job exposure matrix and then the unification of the job exposure matrix with personnel tables is the essential element. There are few, if any, organizations in the United States as well equipped as NIOSH to bring this exposure assessment to a successful conclusion.

Overall, I would judge this proposal outstanding. Were I to review it in the context of an application for support from the National Institutes of Health, it would rank in the top five percentile of all the grant proposals that I have reviewed in recent years.

Davis

I applaud the National Cancer Institute and the National Institute for Occupational Safety and Health for their initiative in undertaking this study to examine the association between mortality, in particular, lung cancer and exposure to diesel exhaust. Diesel exposures are widespread and are of substantial concern not only to the estimated 1.3 million workers who are occupationally exposed but also to the public at large. The potential carcinogenic effects of exposure to diesel exhaust are a significant public health concern that demands further study.

The overall study approach is well conceived and specifically addresses weaknesses in the existing studies regarding the health impact of diesel exhaust. The investigators have targeted a high exposed population, will utilize quantitative estimates of exposure based on current and historical measurements of diesel exhaust, will include information about potential confounding factors and, to the extent possible, adjust for confounding in the analysis. Additionally, the study is of sufficient size and subsequently power. Potential drawbacks include lack of adequate information about potential confounding factors, in particular smoking, most notably for those deceased in the earlier follow-up period (1970s).

Eisen

The cohort study described in this proposal has been well thought out. It is well designed and clearly described. Moreover, the research effort can be well justified in this situation. The weight of the scientific evidence that diesel exhaust is a human carcinogen is strong enough to merit this attempt to better specify the quantitative nature of the risk. This study design is state-of-the-art and the nested case-control approach represents the best possible strategy for examining the relationship between exposure and cancer risk. Moreover, despite the necessary focus on past exposures, the nature of diesel exhaust exposure has not changed over time and thus results will be directly relevant to the assessment of current risk.

The difficulties inherent in doing a retrospective cancer study of lung cancer are well known - adjustment for confounding due to cigarette smoke, reconstructing valid estimates of past exposure, the healthy worker effect - and the investigators have carefully considered each of them and have provided adequate approaches to address them. I can think of no better research team to conduct this highly ambitious research effort.

Moure

The NCI/NIOSH study protocol appears as an excellent design for a study of health effects of Diesel exhaust in miners. It is the first substantial study that proposes a method to quantify Diesel exhaust (DE) exposures for the purpose of evaluating its association with causes of death. It represents sound science. No substantive scientific flaws are apparent in the protocol.

Dement

The overall project approach appears to be sound and the project has potential to significantly contribute to our knowledge of hazards associated with diesel exposures. This is an important area of research and should be supported by NCI and NIOSH.

Mine sites to be studied are appropriate in that: 1) confounding exposures are minimized, 2) the cohort is large enough to achieve reasonable statistical power, and 3) workers with sufficient latency to detect increased lung cancer risks are included. Cohort study methods are appropriate and an excellent process for cohort vital status follow-up is described. Analyses of the cohort data using Poisson regression techniques offers an excellent method for simultaneous adjustment of potential confounders.

The nested case-control approach provides a powerful tool for more detailed analyses including better control of potential confounders and more in-depth investigation of exposure-response patterns. Exposure estimation procedures are generally adequate.

Sokas

In brief, this is an exceptionally strong research proposal that promises to answer a specific research question of critical importance for both occupational and environmental health in the United States and throughout the world. The objectives are appropriate and the study design and methodology is quite adequate to address these objectives. The breadth and depth of the personnel conducting the study are of the first caliber, and the amount of preliminary data that has been gathered is impressive.

Woolston

Having reviewed the findings of many other studies of the effects of diesel exhaust, I can attest to the need for solid epidemiological studies such as yours. Rats and mice, the subjects of many of the published works I reviewed, are poor indicators of how diesel exhaust affects humans. Your study is well designed and will have statistical significance when completed.

We are pleased to know that such an extensive study of human beings for any environmental health risk is being undertaken. It is the difficult but relevant studies such as yours that will give us the best information on the effects of diesel exhaust on our species. Many thanks for your efforts.

Hattis

The proposed project to study the mortality of non-metal miners exposed to relatively high levels of diesel exhaust is an excellent example of state-of-the-art epidemiology, applied to a widespread source of exposure of important public health concern. The study population has been carefully selected to

1) minimize confounding with other known chronic lung hazards (radon and silica), and

2) have large enough numbers of people with long term and relatively intense diesel particulate exposures to provide good statistical "power".

The leaders of the study team are highly experienced and well respected in their fields of epidemiology, industrial hygiene, and biomarker measurements. Overall, the prospects seem very good for this effort to definitively detect and begin to quantitatively measure the lung cancer risks that have been projected (with considerable and continuing controversy) over the years from other studies.

Weeks

Both the cohort study and the nested case-control study are important. The cohort study has the usual strengths of other cohort studies. It mimics experimental studies in that a defined cohort can be observed longitudinally, drop-outs can be identified and their condition evaluated, exposure of each member of the cohort can be calculated, and outcomes can be evaluated. Lung cancer deaths are to be counted not only with death certificates (considering not only primary but also secondary causes of death) but also with clinical and histological evaluation as well. A control group of non-exposed workers is available, thereby avoiding a healthy worker effect bias. All of these are strengths.

The most important contribution of these studies arises from a combination of factors: the opportunity to investigate mortality in a sufficiently large cohort, with (unfortunately) relatively high levels of exposure to diesel exhaust, and with measurements (rather than estimates) of exposure extending farther back in

time than for any other cohort studied to date. Each of these factors should be exploited to the fullest.

Given the relatively modest expected SMR (most < 2.0, but with poorer measurements of lower levels of exposure), these studies are vulnerable to selection bias. Therefore, assessment of both exposure and outcome are critical, a need the investigators have acknowledged and attended to in an exemplary fashion. This is state-of-the-art epidemiology.

Rall

In an oral statement he said that the study protocol is very good, and that the biomarker study is a good step.

Cole/Corn/Mandel

The proposed NCI-NIOSH study offers opportunities to provide further information about the relation between exposure to diesel exhausts and risk of lung cancer. The study's strengths derive from the moderately large size of the cohort and the resultant expectation of over 100 lung cancers, the wide range of diesel exposures, and the reported low levels of exposures to radon and other known occupational causes of lung cancers. However, there are a number of serious limitations which may hinder the evaluation of the role of diesel exhaust in cancer risk. As is often the situation in any single epidemiologic study, even though the investigation may provide information to help clarify the health effects of diesel exposure, the inherent limitations may preclude a definitive assessment of the association at the study's end.

Frank

This overly complex study may not be as helpful as would be hoped, and would take a considerable period of time as well as large sums of funding and has the potential of being inconclusive.

Hall (with regard to the exposure assessment component only)

In summary, there are many aspects of the proposed exposure assessment that require better definition prior to investment of time and effort in the field. The use of area samples to estimate quantitatively occupationally related potential exposures should be discarded. The use of compliance-related exposure estimates should be rethought. A well designed feasibility study should be developed and implemented. Considerable work needs to be done to demonstrate that a valid defensible assessment of historical exposures can be attained. Thought should be given to discarding the attempt to quantitatively estimate historical exposures. It is clear from the industrial hygiene literature that this approach, given the quantity and quality of expected exposure data, is unlikely to provide exposure estimates that will allow for the quantitative stratification of the exposed population. Consideration should be given to a qualitative exposure estimation approach. This type of approach will, more likely, result in a reasonable and defensible exposure stratification and cost considerably less in both manpower and time.

MAIN ISSUES

This section presents responses to the main issues raised during peer review.

Study power.

Since some have expressed concern over the power of this study -- in particular, that the study is too large, the following extended discussion has been furnished in justification and explanation of the chosen strategy.

Power calculations are inherently imprecise. As noted by Breslow and Day[1] in their monograph on the design and analysis of cohort studies, "It needs stressing strongly that power calculations are essentially approximate. The size, age composition, and survival of the cohort will usually not be known with any great accuracy before the study is performed.... Furthermore, the level of excess risk that one decides that is important to detect is to some extent arbitrary." In the diesel study we were at an advantage compared to most researchers in that we had a considerable amount of information on the cohort from the feasibility study. Thus our power calculations are probably more reliable than most.

It is critically important to note that the size of the cohort study was controlled by the need to provide sufficient lung cancer cases for adequate power in the case-control study. For this reason, the focus should not be on the power of the cohort study, but should rather be on the power of the case-control study. The protocol is to be modified to reflect this thinking. The following text concentrates on the power of the case-control study.

The revised protocol will state that the power of the case-control study is 96% to detect a trend in odds ratios from 2.5 to 1.6 and 1.0 for heavily exposed, moderately exposed and low exposed workers respectively, assuming 150 cases of lung cancer and 450 controls, a 5% significance level. This assumes that 25%, 25%, and 50% of workers fall within the heavily exposed, moderately exposed and low exposed exposure categories, respectively. This scenario is consistent with a doubling of risk between high/moderate exposure and low exposure, with 50% of workers in each exposure category.

The decision to use these figures in the power calculation was based on available information, coupled with some reasonable estimates. The feasibility study had indicated that the workforce broke down into the three exposure categories in a roughly 1:1:2 fashion, from high to moderate to low exposures. We adopted those values in the calculation. We used the conventional 5% level for the statistical significance test. The odds ratios were selected on the basis of results from published studies. These tended to indicate a potential risk of about 1.5 associated with diesel exhaust exposure (see tables 2.1 and 2.2 of the protocol). Since our available information showed that mine workers might have considerably greater exposures to diesel exhaust than other occupational cohorts, we increased the postulated odds ratios to 2.5 and 1.6 for the two higher exposed groups. This corresponds to a doubling of risk compared to a 50% increase (2.0 compared to 1.5).

Though our estimate of power appears high, there are a number of issues which merit consideration:

a. The odds ratios that we chose were based on informed estimates. At least one reviewer believes that the risks are lower than we assumed. If this is the case, the power will be considerably less than that stated. For instance, if the trend associated with diesel exposure is

more in line with other published studies (in the range 1.5 to 2.0 as shown in Tables 2.1 and 2.2 of the protocol), the power would drop below 80%.

b. One reviewer has expressed concern that lung cancer cases from the early years of the study (1985 was cited as a cut-off year) would furnish unreliable information on exposures and confounders. He recommended that only cases after that date be included in the study. (We concur that data for early cases will probably be less reliable than for later cases. We propose to explore this issue in the analysis by dividing the data by time period and examining the consistency in the findings.) We have examined the effect of omitting the early cases on the power of the study. If we take only cases occurring after 1985, we lose about 40% of the cases, and the power drops from 96% to about 83%. This value of 83% is marginal, and if the risks were lower than we have assumed in the calculation, it would drop to an unacceptable level.

c. Other factors which we have not been able to take into account impinge on the power calculation as well. Imprecision in the exposure assessments, the inability to know at this stage the exact quality of the work histories, and possible short tenure of some miners, for example, all could act to reduce power.

d. We are concerned with a potential problem with clustering. We have only 10 mines (clusters) in this study. When one has few clusters, it is possible that effects in one or two can dominate the whole analysis, and prevent one from properly assessing whether an effect is generally evident. Hence, to reduce the study size by having fewer mines is not a good idea. This problem is particularly acute in the diesel study because of a skewed distribution in mine size. The only mines that might be eliminated are the smallest (because the loss of a large mine would impinge too much on study power). However, this would mean that the study would be based on a few large mines, and thus very prone to mine-specific effects that may be unrelated to the question at issue.

e. The power calculations, like those for most other studies, are only concerned with main effects. They do not take into account interactions of interest, such as the important one between smoking and diesel exposure. The power to detect interactions is less than it is for main effects, and so retention of the sample size would assist in detection of interactions if they exist.

f. Lastly, the costs and benefits of reducing study power have to be carefully balanced. Very high power would would lead to a somewhat inefficient study. However, power that is too low might lead to a false conclusion regarding worker risk, with a resultant waste of funding and inconvenience to all participating mines. Given these two scenarios, it is prudent to err on the side of too much, rather than too little power.

Exposure assessment methods

At this time there are no published mortality studies in which quantitative measures of diesel exhaust exposure have been analyzed in connection with lung cancer mortality. The few studies where measurements have been taken have not linked them tightly into the mortality analysis. Hence, there is a great need for a definitive study in which estimates of exposure are incorporated into a strong mortality analysis, especially when confounders from other exposures are low or absent.

While we fully intend to derive and employ surrogate indices of exposure (e.g., time in high exposure

jobs, underground versus surface work) in the analyses of mortality, complete reliance on surrogate indices of exposure in epidemiologic analysis is nowadays considered to be less than state-of-the-art if there is the opportunity to derive quantitative exposure indices. As has been said (Stewart, Report on a Workshop to Evaluate the Feasibility of a Computerized Exposure Assessment Program for Occupational Epidemiologic Studies), "Exposure assessment in occupational epidemiology studies is a crucial component when evaluating associations of disease with exposure. Traditionally, development of risk estimates has been based on surrogates of exposures, such as ever/never exposed to the chemical of interest and/or duration of employment or exposure. These surrogates were used because monitoring results were not available. Although these surrogates have been shown to result in misclassification of exposures,[2] they have been successful in finding excess risks. The success, however, is likely to be due, in part, to the large risks associated with such exposures such as asbestos, inorganic arsenic, beta-naphylamine [sic], chromium, and others. It is likely that future investigations must deal with exposures that cause less dramatic increases in risk.[3] If this is the case, misclassification introduced by the use of surrogates for exposures of interest raises concern as to whether associations will be missed...." Another reason for using quantitative measures of exposures is that the study results have immediate application for health and safety.

The job-exposure matrix approach to be proposed in this study (see Summary and Detailed Comments) is by now a fairly standardized and validated approach. As has been said, "In spite of hard criticism, job-exposure matrices have not turned out to be a track of errors in the history of occupational epidemiology. In very large studies, whether of the cohort or case-referent design, the job-exposure matrix approach is often the only feasible way to assess exposure. But there are differences between job-exposure matrices. Their structure varies widely, as does their validity -- from nil to perfect. It is therefore important that the users know how to use the job-exposure matrix and how valid it is for the specific exposure(s) under study. The traditional job-exposure matrices which crudely specify exposure in qualitative (exposed, unexposed) or ordinal (low, medium, high) terms without any further documentation are losing their function, along with the requirements for better quality. Future job-exposure matrices will probably be more like exposure information systems which are quantitative and include accurate definitions and documentation. They can provide quantitative proportions and levels of exposure within occupations or other exposure groups, estimates on the numbers of exposed workers, descriptions of sources of exposure, relevant monitoring results, and bibliographic references, which make them useful also outside etiognostically oriented epidemiology in areas such as quantitative risk assessment and hazard surveillance." [4] It is this concept of the job-exposure matrix that we will be striving for in this study.

Though the technique of retrospective exposure estimation is progressing and being refined, it still requires that informed judgments be made when data are incomplete. For example, it is unusual to find complete exposure data on all occupations over all time periods of the study. In this case, some estimation process has to be used to supply information for those missing groups. The assignment of exposures in these cases is undertaken using all available input, including existing data, the experience of the industrial hygienist, and the opinions of those knowledgeable about the industrial situation. Given that there will be a degree of uncertainty in the derived estimates obtained in this way, it behooves the researchers to be careful not only to document their decision making, but to explore the implications of their decisions by undertaking sensitivity analyses. The latter are designed to permit assessment of the effect of varying the various analytical assumptions and parameters used in the exposure assessment process on the final outcomes from the study. In this study we intend to follow these procedures. Use of the NCI Exposure Estimation Program in derivation of the retrospective exposures provides automatic and full documentation. In addition, we intend to undertake a sensitivity analysis to explore the implications of our assumptions.

Concern has been expressed over validation of exposures in this study. There are two aspects to this issue: the measurements to be undertaken in the current industrial hygiene assessment phase of the project; and the process of retrospective exposure assessment. With regard to the former concern, we will be using sampling techniques currently regarded as state-of-the-art for environmental assessment of diesel exhaust. These include elemental carbon, organic carbon, submicrometer combustible dust, and submicron particulates. Our choice of exposure variables is informed by our own experience, and that of knowledgeable experts. The German government has recently chosen elemental carbon as the index on which to regulate diesel exposures. Recent and current epidemiologic and industrial hygiene studies in Germany, Canada, and the United States have used one or more of these variables to assess level of diesel exhaust. In our own feasibility study we were able to demonstrate clear and unambiguous trends in exposure levels of elemental carbon among employees who were working at different proximity to diesel engines (Ram car, diesel shop, top side, and office: 0.27, 0.04, 0.01, and 0.002 mg/m^3 respectively). We are using several different exposure indices because, to our knowledge, there is no consensus that any single one of these is overwhelmingly superior to the others. When there is no obviously superior exposure variable available, use of several exposure measures will decrease the chance of failing to detect a real effect, if such exists, by the unsuspecting choice of a poor exposure index. On the other hand, if no effect is detected with all exposure indices, it would provide better evidence than use of one index that the substance probably has no effect.[5]

The second concern over validity lies with the process of retrospective assessment. In this study we intend to undertake special studies to assess the relationship between the newer indices of diesel exposure (e.g., elemental carbon) and older measures (e.g., NO_2) for which past data are available. Conversion factors derived from regression models on the data from these correlation studies will be used to adjust the past data to the newer values. The use of factors to adjust exposure values is commonplace in retrospective exposure assessment, and, properly done, supplies valid information. As an excellent example of this, the case of coal mine data in the British Pneumoconiosis Field Research (PFR) is instructive. In this, side-by-side sampling was undertaken in special studies in various areas of each mine using both particle count and gravimetric samplers. The derived relationship between particle count and gravimetric data was used to adjust the large database of historical particle count measurements. The results showed that the derived gravimetric exposures correlated better with response (pneumoconiosis) than did the unadjusted particle counts. It is this approach that we will be using in the diesel study. Information from the feasibility study, in which side-by-side sampling was undertaken in various areas of one mine, demonstrated the ability to correlate older measures with the newer indices. Correlations of NO_2 with elemental carbon were 0.64 for individual measurements and 0.90 after averaging by department.

It should be mentioned that there is usually no 100% effective method for validating retrospectively derived exposures. In many cases, as in the diesel study, there are few past data available with which to compare and assess the extrapolated values. Instead, one must rely on careful examination of the data by assessing agreement with evaluations by those experienced with the various industrial processes and work practices and with those knowledgeable about past conditions. In addition, the coherence of the the mortality analysis results using different exposure indices and surrogates will be a major criterion in evaluating the validity of the derived exposures.

In summary, it is our opinion that the data from these non-metal mines provide a unique opportunity to evaluate the question of lung cancer and diesel exhaust exposure. We are not aware of any other industrial cohort in this country having such high exposures, low levels of confounders, and quantitative historical exposure data. These factors make it imperative that quantitative exposure indices be

generated for the workers and used in exposure-response analysis. We have shown that such exposure derivation is possible, and we have done this using standard techniques and accepted scientific practices. We are committed to full exploration of the implications of the derived exposures, including sensitivity analysis and open and full documentation of our methods.

DETAILED COMMENTS

This section is divided into subsections corresponding to the main divisions of the protocol: Summary, Background, Feasibility Study, Study Objectives, Cohort Study, Case-Control Study, Biomarker Study, and Exposure Assessment. Each entry consists of a quotation or paraphrase of the issue raised, followed by a response. In some cases, related points are grouped and one response given to all. The following individuals, groups, or institutions provided comments; in the text, each comment is prefixed with the indicated abbreviated name for brevity. Please note that page, paragraph, and section numbers refer to the August 9, 1995 version of the protocol submitted to the Board of Scientific Counselors for discussion on January 14, 1997.

SECTION 1 - SUMMARY

Corn/Cole/Mandel

Comment: "The paragraph is somewhat ambiguous in its use of the word 'risk' followed by a statement regarding the need for information on the 'quantitative relationship.' The erroneous implication is that there is an established causal relationship for which only exposure-response information is lacking when, in fact, the causal nature of the association has not been established."

Response: On page 4, paragraph 2, we clearly state that "the risk of lung cancer in humans is still not well defined." In addition, neither the word cause nor causal appear in the protocol in connection with diesel exhaust and lung cancer.

Cole/Corn/Mandel

Comment: "A reference to the IARC categorization of diesel exhaust should be included. The information available does not indicate that IARC has classified diesel exhaust in category 2B. Further, the National Toxicology Program does not list diesel exhaust even as a suspect carcinogen."

Response: Both in the summary and elsewhere we say that The International Agency for Research on Cancer (IARC) has classified diesel exhaust as a probable carcinogen (which is a 2A (probable) not a 2B (possible) classification). The point of the paragraph was not to list every organization which does and does not list diesel exhaust as a carcinogen, but to make the point that despite certain current authoritative statements, further information is still necessary.

Cole/Corn/Mandel

Comment: "A first reference is made to the biomarkers study. But neither here nor elsewhere is the need for such a study developed adequately."

Response: A monograph from a recent IARC workshop attended by scientists from academia and government on methodologic issues in the use of biomarkers in cancer epidemiology noted that "..in the presence of limited epidemiologic evidence of a chemical's carcinogenicity, the demonstration in humans that the chemical causes a dose-dependent increase in macromolecular adducts or in other biomarkers that reflect genotoxic damage provides supporting evidence that the chemical is carcinogenic to humans[6]. See p. 37 below for responses specific to the biomarker component.

Cole/Corn/Mandel

Comment: "The exposure assessment proposed as a feasibility study requires validation. In view of the concerns expressed later in this report, it would seem prudent to resolve the issues before proceeding with the study."

Response: Information from the completed feasibility study will be provided as an appendix to the revised protocol. Validation of the exposure measures is discussed on p. 11.

Cole/Corn/Mandel

Comment: "Why not wait to see if diesel exhaust is, in fact, associated with lung cancer before starting the biomarker study?"

Response: Four reviewers supported the biomarker study while two were opposed (p. 37). We believe that having the results of the biomarker study at hand when the findings from the mortality studies are complete will enable the findings and implications of both to be interpreted better. We also gain cost efficiency in the study by doing the biomarker component at the same time as the mortality study. For further information on this, see p. 37.

SECTION 2 - BACKGROUND

Cole/Corn/Mandel

Comment: "The investigators should address the naturally occurring dusts in the mines in addition to the sources for elemental carbon either through the mining of the ore or through the use of explosives whose by-products may compound the exposure assessment."

Response: The text to which they refer is concerned only with diesel exhaust exposures, their composition, and their effects. It was not the intent at this stage to mention specific environments, elemental carbon, nor other dusts. The point raised is legitimate, however, and is addressed in the various places in the protocol and in these responses (e.g., p. 27 for confounders).

Hattis

Comment: "P. 6. 1st par. I think diesel exposure is of potential concern for the general population, but I don't think the stress on the two-fold difference in air levels between highways and residential areas is of particular significance. If you add up the hours spent commuting in comparison with the hours spent 'in residential areas' the commuting exposure is unlikely to make a material difference, with the possible exception of long haul truckers. Also, it might be said that there is a considerable difference in the exposure levels for general residences and the mines to be studied. The relevance of the study for assessing general population risks will be at least as much in understanding relevant mechanisms of action of diesel particulates (and hence dose projection rules) than in the likely direct positive findings of carcinogenic and/or other activities. Overall, I think the authors could do without the last two sentences here. Additionally, 1.34 million workers exposed is likely to be entirely too many significant figures in the absence of careful specification of what 'exposed' means. I think it would be sufficient to say that somewhat over a million workers are likely to be significantly exposed over background general population levels, if the available data will support that much."

Response: We will change "1.34 million" to "over 1 million" in recognition of the probable imprecision in our original statistic.

Hattis

Comment: "P. 7, 3rd par. In addition, or perhaps in place of Table 2.1. I would suggest citing or reproducing the meta-analysis presentation of the previous cohort and case control epidemiological studies done by Aaron Cohen in the HEI report. The advantages of this is [sic] the inclusion of confidence limits for the individual studies and the quick visual sense that one gets of the overall results."

Response: We feel that the information in Tables 2.1 and 2.2 of the protocol provides sufficient detail for assessment of published findings. The tables also include results from studies not cited in the Health Effects Institute (HEI) report.

Hattis

Comment: "P. 7, last par. I would not be as negative on all the previous epidemiological studies as is implied here. And I think it is a little unfair to say of the Garshick study, for example, that 'none had developed quantitative estimates based on measurements of diesel exhaust.' Tom Smith as part of that study in fact did a rather extensive series of measurements, although without NIOSH's carte blanche access to workplaces, he was unfortunately limited to a small number of currently operating railroads. Later on I believe the document makes a fuller explanation that the Garshick study used measurements in these few places to do an approximate assessment of diesel exposure levels that might have been associated with specific job titles, but without a detailed workplace-by-workplace review of the exposure records for the deceased employees that showed up in their source of mortality information. It would be good to give appropriate credit to the efforts of prior researchers to quantify exposure while not minimizing the important advances promised by the proposed non-metal mineworker study."

Response: The text will be changed accordingly.

Hattis

Comment: "P. 13, 1st par. I would have liked to see some more detailed data from Phase II of the feasibility study, possibly in another Appendix. Also what exactly is meant by 'heavily exposed' and 'moderate to low levels of exposure'? Such qualitative terms are needlessly imprecise."

Response: We now will include information from Phase II of the feasibility study in the Appendices. We will also qualify what we mean by high exposure etc. Generally, high exposure applies to those workers working near to, or downstream of, where large diesel equipment is being used (e.g., ram car operators). In this respect, it typically refers to face workers, as opposed to those working elsewhere in the mine. Moderate exposures would be experienced by most other underground workers (e.g., general maintenance workers), and also a small proportion of surface employees who work with, or near, to large diesel equipment.

Epidemiologic evidence

Cole/Corn/Mandel — Comment: "Reference should be made to a short follow-up period, not to a short 'latent' period. The term 'latent' is prejudicial as it implies that there is an effect."

Response: We agree that "short follow-up period" is more appropriate and will make changes to comply with this.

Summary of published studies

Cole/Corn/Mandel — Comment: "Several studies are commented upon as being of 'low power.' But, low power, or precision is an irrelevant criticism to offer of a series of studies unless they are collectively imprecise. It seems clear from table 2.1 that the follow-up (cohort) studies are negative."

Cole/Corn/Mandel — Comment: "The results of the case-control studies are mixed to slightly positive. A discussion of some of the weaknesses of these studies and a detailed effort to reconcile the follow-up and the case-control studies would be helpful."

Howard, MSHA — Comment: "Despite problems involving insufficient latency, exposure uncertainties, and lack of statistical power to detect excess risk, 14 of the 18 cohort studies indicated some excess risk. We suggest that you point out that although weaknesses in the studies make it difficult to draw reliable quantitative conclusions, taken together they seem to qualitatively demonstrate a positive association."

Response: These comments are evidently contradictory. With regard to including more material and debate on the pros and cons of the different studies, we disagree. The protocol is not intended to be a detailed review of the scientific literature, nor a debate on the relative merits of different studies and approaches. Such documents already exist.

Summary of epidemiology

Howard, MSHA — Comment: "Weak evidence of excess risk should not be confused with a weak or 'moderate' increase in risk. Although an epidemiological estimate of relative risk equal to 1.5 may constitute weak evidence, a fifty-percent increase in risk is substantial, if it actually exists."

Response: We concur with this point.

SECTION 3 - FEASIBILITY STUDY

Cole/Corn/Mandel — Comment: "... More information should be provided on the criteria and the methods to establish the adequacy and completeness of the records."

Response: Appendix B is being revised to describe better the criteria and procedures used in the selection of mines..

Cole/Corn/Mandel — Comment: "The quite high current level of NO_2 and elemental carbon for some underground areas at the single mine monitored in the feasibility study suggest that, if this mine is typical, the cohort should have a wide range of exposure to diesel exhaust. This is a key strength of this investigation, enhancing the power of any assessment of dose response. The possibility that the one mine sampled is atypical should be ruled out."

Response: From comparison of prior data for the sampled mine with those of other mines it does appear that it was fairly typical. Hence, the wide range of exposure will indeed assist in detection of any exposure-response relationship. (It should be noted that the main point of the feasibility study was to examine the correlation between assessments of diesel exhaust using elemental carbon and other state-of-the-art techniques and older measures, such as NO_2. For this to be done adequately, there is no need for the mine to be typical.)

Cole/Corn/Mandel — Comment: "Because radon is such a potent lung carcinogen, it should be confirmed that the low levels prevail throughout the selected mines."

Response: On p. 29 of the existing protocol we say that, "Sampling for radon will be conducted at each area sampling location to confirm the reported low levels of radon exposure.

SECTION 4 - STUDY OBJECTIVES

Cole/Corn/Mandel — Comment: "Objective I) implies that causes of death other than lung cancer will be evaluated, yet no rationale for this is provided."

Response: We will follow commonly accepted procedures for analyzing multiple causes of death, including the division into *a priori* and *a posteriori* groups. See p. 20 for further information..

Cole/Corn/Mandel — Comment: "What other 'potential confounders' will be included in the mortality analyses and how will these be ascertained?"

Response: The principal other potential confounders are silica exposure and radon exposure. These will be dealt with using standard mortality analytical methods, such as use of dummy variables in modeling, analysis of sub-groups, etc. Page 27 provides more information on this.

Gibbs — Comment: "It is therefore crucial that the study protocol is carefully designed to assure that ... all proposed mechanisms of carcinogenesis are evaluated ..."

Response: Two major mechanisms of carcinogenesis are discussed in the protocol: particle overload and mutagenesis by polycyclic organic matter adsorbed onto particles. The biomarker component of the study is included in this overall study proposal specifically to provide insight into this question.

Hattis — Comment: "P. 14, top of page, end of section 4, I would add as a fourth aim, to

collect biological samples for later analysis of somatic mutation frequencies for genes along established molecular pathologic pathways to cancer."

Response: We hesitate to add another objective to the study at this late stage in its development. However, the availability of tissue samples may make it possible to undertake a study in the future.

Howard

Comment: "It states that the latency period for the cohort ranges from 16 to 45 years. It would be interesting to know what the latency period distribution of the cohort is and what would be the shortest latency period that cancer would be expected to be shown in this cohort due to exposure to diesel particulate."

Response: We will not be in a position to tabulate the potential latency in the cohort until data collection is complete and analysis begins. (We would like to note that the protocol is to be modified regarding the statement of latency from '16 to 45 years' to 'up to 46 years').

Frank

Comment: "It is unclear why a simple collection of death certificates and ascertainment of the causes of death was not considered as a first step. Such a straightforward assessment could be done more quickly and cheaply, and depending on the outcome would then either justify, or not justify, the other expensive aspects of this study. One might also ask why a retrospective-prospective cohort study was not considered as an alternative. Given that these miners have been exposed for some 16 or more years, a past assessment of causes of death and a prospective portion added on over some 3 to 5 years might better answer the central question and allow for individual collection of smoking histories, prior work history, and the like."

Response: We interpret this comment to mean that a simple cohort study should be done first. If that indicates an elevated risk of lung cancer among workers who are in the higher exposed groups (presumably based on some surrogate measure), the other parts of the study detailed in the protocol should be done. We find this to be an unsatisfactory course of action. A study of this type would be essentially little different to those shown in Table 2.1, and, though still useful, would not be a major contribution to the literature on diesel exhaust exposure and mortality. Moreover, various organizations, including IARC, NIOSH, and HEI, have concluded that there is evidence of a risk associated with diesel exhaust exposure. For this reason, we feel that a move directly to an exposure classification study is appropriate, and is urgently needed by the scientific community. We will modify the protocol to emphasize this point.

The suggestion of a retrospective-prospective study is interesting, but we are not prepared to commit to a prospective study at this time. However, are modifying the study to include workers who worked after 1979 (to take advantage of the potential for future follow-up). Though we feel that we are currently in a position to undertake a valid and reliable analysis of mortality and diesel exposure, and that the study should not be delayed, we fully affirm that a prospective period of monitoring and follow-up would provide additional

information that would supplement the retrospective findings considerably.

Chajet

Comment: "As the cohort study is proposed there will be a significant demand on the time and resources of each mine to support NIOSH personnel conducting the exposure assessment phase of the study. Also there are significant questions concerning the analytical methods proposed to assess current exposures as well as the methodology that would be used to reconstruct past exposures. The MARG coalition believes that there is an alternative that could accomplish the same goals but which would be far less imposing on the mines. The alternative would also allow time for industrial hygiene retrospective assessment and analytical issues to be resolved. The cohort study could be completed without a retrospective exposure assessment. The study group could be divided into "above ground" and "under ground" groups for comparison (or some other qualitative grouping). Concurrent with the cohort study, the analytical methods for assessing diesel exhaust exposure could be refined and the methodology for doing retrospective exposure assessment could be piloted at mine locations. A rigorous exposure assessment could then be done as part of the case-control study which would be limited to a much smaller number of workers and would be more manageable for both NIOSH/NCI and the mine operators. The alternative approach should provide equivalent information, quicker results and lower costs to NIOSH/NCI."

Response: We feel that this approach is both unsatisfactory scientifically and also unlikely to lead to significantly less imposition on the mines. As noted above, current epidemiologic thinking is that quantitative exposure assessment be done whenever it is realistically feasible and likely to lead to reliable estimates of exposure. As outlined above, we feel that this is the case for this study. We have noted that the exposure variables to be used are accepted by the scientific community, and demonstrated that we are able to obtain the good correlations for retrospective assessment. Hence further extensive piloting and testing of the research methods is not required.

With regard to cost savings and inconvenience to the mines, we point out that the exposure assessment for the case-control study would probably require as much effort as sampling for the complete cohort. The miners in the case-control study would have worked in many jobs; exposure assessments would have to be made for each of those separate jobs. Hence, overall, we may have to derive exposure levels for most jobs in the mines, requiring an industrial hygiene survey of about the same extent as that needed for the cohort study exposure derivation.

Lastly, one of the strengths of the study is the ability to compare the findings between the cohort and case-control studies. Comparison will provide an internal evaluation of the coherence of any effects and relationships. Without exposure data for the cohort study, this evaluation will be weakened considerably.

Based on these three arguments: scientific, cost saving, and evaluation of coherence of findings, we do not find the above proposal to be a satisfactory

alternative to the approach laid out in the protocol.

SECTION 5 - COHORT STUDY

General points

Gibbs

Comment: "The study protocol should be modified to take advantage of any pre-dieselization data available... A pre- and post-dieselization study would control for all confounders except time period."

Response: We do not think it is feasible to make this change, since many of the study mines started operation the same year as, or very shortly before, dieselization, as shown in the table below.

MINE #	COMMODITY	FIRST ACTIVE	YEAR OF DIESELIZATION
Primary Mines			
6	TRONA	1967	1967
7	TRONA	1962	1962
8	TRONA	1949	1965
13	SALT	1959	1960
15	LIMESTONE	?	1960
16	POTASH	1964	1964
18	POTASH	1952	1952
19	POTASH	1964	1964
21	POTASH	1940	1950
23	SALT	1898	1962
Back-up Mines			
2	LIMESTONE	1947	1948
12	SALT	1962	1963
17	POTASH	1930	1950
24	SALT	1948	1950

Davis

Comment: "P.16. Investigators state that the latent period will range from 16 to 45 years. This is incorrect. Theoretically, a subject could have entered employment in 1978 and died in 1980, in which case the latent period is less than two years. This can be addressed in the analysis by stratifying by latency period (time between entry into industry and death). Results by latency period can provide important insight into potential associations."

Response: This is correct, and we will modify the text accordingly.

Causes of death to be analyzed

Eisen — Comment: "The emphasis on lung cancer is reasonable in light of animal and human data reviewed in the Background section. It is also reasonable to examine SMRs for evidence of excess risk due to other causes of death. However, there is no background discussion of any other suspected health effect - except for a brief mention of bladder cancer. How consistent is the evidence for bladder cancer? Are there any other cancer sites of particular interest? Are nonmalignant respiratory effects also suspected?"

Davis — Comment: "P.15. What causes of mortality will be investigated? These should be specified a priori and consistent with current findings/hypotheses regarding diesel exhaust."

Response: We will follow the approach taken by most researchers conducting cohort studies. The scientific literature on diesel exhaust exposure has shown evidence of excess mortality from certain causes. These will be treated as *a priori* hypotheses. We acknowledge that the power of the study for each ancillary cause of death may be less than optimal. However, it would not be prudent to ignore these data. Finally, *a posteriori* elevated death rates due to other causes will be investigated in the context of hypothesis generation. The case-control study will examine only lung cancer. If other causes of death appear worthy of further study, separate protocols will be developed for this purpose.

Criteria for inclusion in the study cohorts

Cole/Corn/Mandel — Comment: "Why does the intake period stop at 1979. [sic] The cost of extending intake to, say 1989, would be modest and these more recent workers may prove to be of value."

Weeks — Comment: "First, the follow-up period to 1979 is unnecessarily too short. A longer follow-up is possible and necessary: there is no reason not to follow this cohort for as long as possible. In both the Harvard study of rail-road workers and in the Lovelace studies of rats, there is a long latency and a non-linear exposure-response relationship with the frequency of lung cancer deaths or tumors increasing rapidly late in each study. In fact, a principal reason for prior studies showing negative results is because of follow-up that was too short."

Eisen — Comment: "To be eligible, a worker must have worked at least one year during the period from when diesel use began to 1979. Although reasonable, one wonders why 1979 was chosen, for example, rather than 1989. In terms of obtaining reliable and complete data on cigarette smoking in the case-control study, more recent cases would be easier to locate."

Response: The reviewers' comments were adopted and the intake period

increased to December 31, 1996. The main purpose for doing this was to supplement the cohort in case further follow-up would be desirable in the future. As noted, the additional cost of doing this is marginal, compared to the benefits.

Rall

Oral comment: He questioned whether the duration of the follow-up time is long enough to determine if lung cancer occurred.

Response: We have up to 46 years of time from first exposure to end of follow-up. This is longer than for most published studies and is reasonable since the mean latency period for lung cancer is 15 - 20 years.

Inclusion of workers with little or no exposure

Howard

Comment: "Since many workers included in the cohort are expected not to be occupationally exposed to diesel exhaust, the minimum period of exposure is zero. It would be helpful to explain why it is important to include workers with little or no occupational exposure in the cohort."

Response: The unexposed workers are included to allow for analyses comparing exposed and unexposed workers. Use of an internal reference group can help solve problems of confounding encountered with the use of external reference populations.

Mine Selection

Cole/Corn/Mandel

Comment: "What criteria will be used to determine the "quality" of the records? What, if any, steps will be taken if the records are deemed to be of low quality? How might this affect the study?"

Response: Determining the quality of personnel records was part of the function of the feasibility study. During the feasibility study, site visits were made to estimate the total number of personnel files kept by the mine and to microfilm a random sample of between 10 to 15 percent of the personnel files. Results from the feasibility study samples of personnel records showed that for the 14 mines selected, the worker's name was on 100% of the records, the social security number was on 96% to 100% of the records and the date of birth was on 98% to 100% of the records sampled. Department and job titles, dates of job changes, work history prior to mine employment (from employment application forms), and names of next of kin were available from the personnel records of all the 14 mines. Only those mines with satisfactory records were retained in the study. After the main record collection phase, poor quality records will be deleted. Poor quality records consist of those with inadequate identification or work history. Although deletion is expected to be random, and thus will not cause bias, analyses will be undertaken to check on patterns that might suggest non-random groups of poor or missing data.

Hattis

Comment: "P. 14, last par. Was there a specific ranking formula that weighed the different factors in a particular way? What was it?"

Response: This refers to the criteria for mine selection. An appendix will provide extensive information on this point in the revised protocol.

Information on smoking

Cole/Corn/Mandel — Comment: "What smoking information would they expect to find in the personnel record? How complete will it be? What do they propose to do with it? It is unlikely that standardized data will be available on smoking practices at the time the records were created and it is unlikely that smoking histories will be uniformly available."

Gibbs — Comment: Expressed concerns about smoking information available from personnel files.

Weeks — Comment: "The other weakness of the cohort study is its relative inability to account for the most important confounder of all lung cancer studies, cigarette smoking. This problem can be, and is planned to be addressed with the case-control study. With a smaller group of workers or the families of workers, it is feasible and cost-effective to determine smoking habits of cases and controls and to make the appropriate adjustments."

Eisen — Comment: "Because the estimates of lung cancer risk in other studies are small (<2.0) in relation to the relative risk due to cigarette smoking, some attempt to control for smoking beyond the Axelson adjustment is necessary. The intention to capture smoking information in interviews of cases and controls is the only reasonable approach."

Davis — Comment: "Include more information about 1976-78 NIOSH/MSHA morbidity study. How many workers were involved? This is relevant to understanding extent of available information on smoking in study population. This information is key to both the cohort study, in which data on the prevalence of smoking in the study population are necessary to apply the Axelson method of adjusting for confounding and in the case-control study where individual smoking histories are necessary."

Response: In occupational studies there is ample evidence that smoking does not confound well designed cohort studies of lung cancer risk.[7] In addition, Table 2.2 of the protocol shows almost identical findings on average for case-control studies not adjusted for smoking compared to those where adjustment was made (OR=1.7 (n=13) not smoking-adjusted versus OR=1.8 (n=21) for smoking-adjusted). (The sole cohort study which had smoking adjustment gave rise to SMRs generally greater than those for the non-adjusted studies.) Even if there is evidence of potential confounding, steps can be taken to control for this in the cohort study. For adjustment using the commonly-employed Axelson method in the cohort study, we will employ data from the 1976 NIOSH/MSHA morbidity study supplemented with information gleaned from personnel files, if useful. With regard to the percentage of the cohort with smoking information, there is smoking information for 70% of the mines (seven of the ten mines had smoking

data ascertained during the 1976 morbidity survey). Apart from this, there is extra information on six other non-metal mines from the 1976 morbidity study that is relevant to this question. In total, there is information on 2,140 miners from the morbidity study. The feasibility study sample showed that some smoking information was available for 7 of the 10 primary mines and two of the four back-up mines. For estimates of the U.S. population smoking habits during a period towards the earlier part of the study period there are Health Interview Survey data collected by the National Center for Health Statistics in 1965, 1966, 1970, 1974, and 1978. The case-control study, of course, will be able to adjust directly for smoking.

Data abstraction

Cole/Corn/Mandel

Comment: "This suggests that they will obtain work histories prior to employment in the study mines. They should explain why and how they propose to do this. How complete are prior job histories? What will be done for past mine employment, particularly in view of the high turnover rates in the mines?"

Davis

Comment: "P.17. The proposal to obtain information on previous work histories and smoking from employment records appears overly optimistic. Elaborate on finding from the feasibility study, and the types of records that will be searched, e.g. job applications, medical insurance records."

Response: Pre-employment questionnaires on job application forms will be used to obtain work histories prior to employment in the mines. For those individuals who had worked in more than one of the study mines we will use records from all mines to compile the work history. The feasibility study showed that all the study mines had job applications in the personnel folders. Prior mine work, based on pre-employment records, will be assessed and considered in the analysis.

Gibbs

Comment: "...an occupational history after leaving the study mine's employment is critical....."

Davis

Comment: "P.20. While [sic] is useful to account for potential exposure to diesel in jobs outside of mining, it should be acknowledged that, in the cohort study, this information is available only for those jobs that preceded employment in the mines."

Response: It is true for all retrospective cohort studies that there are gaps in the work-history information after workers leave the study mines or plants. Typically, this cannot be avoided. For any study, the extent of the missing information will vary among the cohort members and can only be ascertained once the cohort is assembled. Workers who retired from the study mines during the course of the study will have no gaps. Miners who moved between the study mines may also have no or small gaps.

Using information from the MSHA/NIOSH 1976 study in these mines, we have

explored the extent to which the nonmetal miners had previously worked in metal mines (where silica, radon, and arsenic exposures would likely be prevalent). A tabulation of the work histories, which were complete for each of the 2,140 participants (having been elicited by personal interview), showed that only 10% of the study participants had worked in metal mines. Of these, half had worked in face jobs. Moreover, the time spent in metal mining was generally short, amounting to five years or less in 70%. Together, only 46 individuals, or 2% of the total, had spent more than five years in face work at metal mines prior to working in the non-metal mines. Fifty percent of the metal mine jobs reported were in copper and lead mines. Prior work in uranium mines accounted for only 6% of all jobs.

We also looked at prior work in nonmetal mines for miners in the metal mine segment of the 1976 study. This showed only three job reports of prior work in non-metal mines (2 years, 4 years, and 21 years, respectively). This indicates that migration from non-metal mines to metal mines was minimal among the participants in the 1976 morbidity study.

Cole/Corn/Mandel

Comment: "Double extraction of all the records may be unnecessary. A sampling strategy for validation would be less expensive."

Response: Our current practice is to abstract information directly from records to the computer database using two clerks working independently, with differences being resolved by the supervisor. Double extraction gives us information of higher quality.

Determination of cohort eligibility

Dement

Comment: "Page 18. Use of the SSA files for the cohort completeness check is not well described and needs more elaboration. For example, will all mines be included or only a sample of mines? Which mines are to be included and how will these be selected?"

Response: We do not currently know how many mines would participate in requesting SSA records. All in all, we think that this procedure is a desirable adjunct to, but not an essential component of, the study.

Cole/Corn/Mandel

Comment: "How will the completeness of the cohort be determined if Social Security Administration records are not available"

Response: We will collect payroll records and seniority lists for the time-span of the study from the company and/or the unions, where available. We will use these lists to make a systematic computerized check of the completeness of the personnel records. The mine administration will be queried if some personnel files appear to have been missed during the record collection site visit, and the records copied. If the records cannot be obtained, we will at least know the extent of missing records. Some missing data can be tolerated, since there may be little bias introduced in an assessment of cause-specific mortality by including

mines with missing data.[8]

Follow-up procedures

Cole/Corn/Mandel — Comment: "...some comment should be given to the likelihood of complete ascertainment in the early years (particularly the 1950s-through 1970s) of follow-up."

Response: For each study mine, the start of follow-up is, at the earliest, one year after the date of dieselization. The dates of dieselization in the primary mines are shown in the table given near to the start of this section. Of these ten mines, only two began using diesel in the early 1950s, while the other mines began in the early to mid 1960s. Thus only a very small portion of the cohort may have died during the 1950s. After 1962, the probability of finding someone who died after age 60 is better than 80%. In many cases the reason for failure to ascertain vital status lies not in the absence of the record but in the lack of precise information for retrieval. One can improve the chances of finding a person by trying various combinations of spelling of the name. For deaths occurring in 1979 or later, the National Death Index is between 93-98% effective at identifying known decedents. As stated in the protocol, we will use a number of different sources to trace hard-to-locate individuals, e.g., postmasters, credit bureaus, and, for the most difficult cases, contact of family members.

Frank — Comment: "It might have been helpful if the investigators had explored the possibility of using union records to obtain mortality information in those settings where mines may have been unionized. At least a comment as to this consideration would have been useful, even if the mines had not been unionized."

Response: This point is valid, and we will modify the protocol accordingly. In an ongoing mortality study of coal miners being undertaken by NIOSH, union records were very helpful in tracing individuals.

Mine-specific analysis

Gibbs — Comment: "Analyze the cohort data by mine....."

Response: We intend to stratify the analysis by mine to examine consistencies and inconsistencies in the findings.

Indices of exposure to diesel exhaust

Cole/Corn/Mandel — Comment: "What is meant by "lagged" estimates and how does this relate to "latent period"?"

Response: As noted by Checkoway,[9] "A fourth technique for avoiding exposure and follow-up overlap is to *lag exposures* by some assumed latency interval (y), such that a worker's current person-year at risk is assigned to the exposure level

(either intensity, duration, or, most commonly, cumulative exposure) achieved *y* years earlier." Several different lag periods can be chosen for investigation. It is an attempt to differentiate between the exposure received between the time of first exposure and disease induction, and the exposure received after disease induction but before the case or death is identified, this latter exposure not being relevant to the analysis.

Hattis — Comments: "P. 17, section 5.D.1. As indicated in my general comments, in addition to arbitrary lag periods, I would suggest developing weighted exposure indices based on alternative hypotheses about the stage of action of diesel particulates in a multi-stage cancer model."

Response: Our primary epidemiologic analysis will include investigation of exposure duration, cumulative exposure, and latency. Subsequently, we may explore more complex models using weighted exposures.

Sokas — Comment: "Care should also be taken not to dilute the group by including individuals with insufficient lag time from exposure."

Response: Individuals will be included in the study if they have worked at least one year. The question of time from first exposure to end of follow-up will be dealt with in the analysis.

Cole/Corn/Mandel — Comment: They discuss factors that will lead to inaccuracies in exposure assessment for individual workers, and say all that the potential errors will be compounded. "This aspect of the reliability of the exposure estimation is not addressed in the proposal."

Response: The variability inherent in estimation of worker exposures is a recurring issue in epidemiologic research. Yet, despite this, studies have been able to demonstrate exposure-response relationships. There is no reason to believe that this study should be worse, and good reasons to believe that it will be better in this respect. We will, in any case, be conducting a sensitivity analysis to examine the effect of varying the major factors and parameters employed in the retrospective exposure assessment.

Confounding from other exposures

Cole/Corn/Mandel — Comment: A question in regard to the levels of radon, silica and arsenic, and what criteria we will use to determine the levels are below those which might be expected to cause confounding. "What is meant by 'unforseen elevations' and how will the investigators determine if confounding 'appears to be a problem.'?"

Cole/Corn/Mandel — Comment: "In the regression analysis, it is proposed to include in the model information on asbestos, radon, arsenic and silica if necessary. The investigators should explain what they mean by 'if necessary'."

Gibbs — Comment: "Determine expected excess lung cancer risk in the cohort population

due to silica and radon based on prior NIOSH or EPA risk assessments and the average exposure levels in the study mines."

Dement

Comment: "Page 20. Poisson regression: Treatment of potential confounders is not well addressed. For example, how will mine and job exposures to confounders be entered into the regression models? While categorical treatment of confounders may allow a first level of analysis, more quantitative analysis of exposure to confounders such as radon and silica may be needed. This has not been addressed in the exposure reconstruction part of the protocol."

Eisen

Comment: "I am somewhat concerned about the possible confounding due to silica, radon, arsenic, and asbestos. Should any of these be found to be prevalent, it will become critical to include this information in the exposure assessment. I don't know enough about these work environments to know how likely a problem this is and how well these exposures could be documented in the past. It would be useful to see a description of how personal exposures to these agents would be in comparison with the primary exposure."

Response: The mines selected for study have been documented as having low levels of exposure to radon, silica, arsenic, and asbestos, and thus confounding by these exposures is extremely unlikely to be a problem. However, to be sure, we will measure these substances during the IH surveys and examine the data for elevations and for correlation of the measurements with the exposures of interest. Analyses will be undertaken with and without controlling for these variables in the statistical models, in order to assess any effect of these potential confounders. In addition, if these exposures are restricted to certain subgroups of workers it might be appropriate to omit those workers from the analysis.

Cole/Corn/Mandel

Comment: "How will employment in other jobs with diesel exposure be taken into account?"

Response: We will examine pre-employment work histories for indications of other jobs with diesel exposure, such as truck driver, bull-dozer operator, etc. Indicator variables will be created to reflect such exposures and employed in the analysis.

Cole/Corn/Mandel

Comment: They questioned the possibility of confounding by socioeconomic status... "particularly in view of the inclusion of administrative workers who are likely to constitute the baseline ('non-exposed') group."

Response: We have decided to exclude the administrative workers from the cohort due to the concerns expressed about the effect of socio-economic status differences between the administrative workers and other mine workers. The surface workers comprise the main group of non-exposed workers. The exclusion of the administrative workers will not greatly effect the size of the internal reference group.

SMR analysis

Gibbs

Comment: "...should pre-determine which reference population will be considered primary with regard to final interpretation of the Cohort Study."

Response: The purposes of the cohort study are to identify causes of death that are elevated in the diesel exhaust-exposed cohort in comparison to both the internal nonexposed cohort as well as external standard populations, and to run trend analyses with regard to extent of diesel exhaust exposure. The internal nonexposed group will be the primary comparison population. Standardized mortality ratio analyses using external reference populations are a standard method of cohort analysis and will be run to allow comparison of results both with those of the internal reference group and with those of other cohort mortality studies.

Gibbs

Comment: He would like the reference population adjusted for smoking status, blue collar/white collar status, mining occupation, and would like to know how endpoints are established.

Response: Use of the internal reference group as the primary reference group will address these concerns. For U.S. reference population comparisons we will adjust SMR's for smoking using the Axelson indirect adjustment as described in the protocol. Death certificates are used for all the reference population death rates.

Hattis

Comment: "P. 18, 3rd par. I am very happy to see that NIOSH will use an occupational referent population (LTAS) that will presumably avoid the tiresome repetition of the finding of a 'healthy worker' effect, and the consequent obscuring of excess risks in the study group."

Response: The NIOSH Life Table Analysis System (LTAS) will be used for analysis. The NIOSH/NCI Computerized Occupational Referent Population System (CORPS) rates will be used in addition to U.S. death rates.

Hattis

Comment: "P. 5, 2nd par., 2nd sentence. As indicated above, I would also include estimates of internal dust exposure and time at exposure/dose as part of the standard mortality ratio analysis."

Response: We will consider including these in our analyses.

Modeling

Cole/Corn/Mandel

Comment: "Explain the use of 'biologically-based mathematical models.'"

Hattis

Comment: "Biologically based cancer models--such as the classic Armitage-Doll multistage model--should have a more prominent place in the authors' planned analysis of their data."

Response: Biologically-based mathematical models of carcinogenesis are models which incorporate biological theories of the mechanisms of carcinogenesis. As

Mazumdar et al.[10] have noted, "Recent literature on epidemiologic studies of human cancer indicates that the Armitage-Doll multistage model of carcinogenesis can be used to examine the relationships of excess cancer mortality to some carcinogenic exposure and time related variables such as age at initial exposure; duration of exposure and time since exposure terminated." In the multistage theory, a cell progresses through a series of ordered and irreversible stages. The multistage model provides information on whether more than one stage is dose-related, and assists in determining at what stage the carcinogen acts. Mazumdar et al. go on to note that Moolgavkar and colleagues have developed a two-stage model that allows for the influence of exposures on cell growth and differentiation as well as on the first mutational event that results in an intermediate cell and the second mutational event that completes the transformation to a malignant cell.[10] Stayner et al. applied amongst other models, both multistage and two-stage biologic models to a study of lung cancer among workers exposed to cadmium to illustrate the modeling methods.[11] Our intention is to first undertake a mortality analysis using conventional techniques and methods (SMR, survival analysis models, and Poisson regression). Subsequently, the data may be employed in a risk assessment analysis using biologically-based models.

Power calculations

Howard

Comment: "How sensitive are the power calculations to the distributions of the cohort's duration of exposure, age and latency period?"

Response: The power calculation is based on actual data from the feasibility study, and consists of far more information directly pertinent to the cohort than is usually available for most proposed studies. Based on this, we expect 120 lung cancer deaths in the complete cohort under the null hypothesis of no effect of diesel exposure for an estimated 184,189 person years of follow-up. In view of the number of records sampled, this estimate is believed to be reliable, and sensitivity is not a major concern. The actual cohort size is expected to be somewhat larger than 8,200, due to offsite records not accessed during the feasibility study (no estimate of how much larger can be made at this time). Extension of the inclusion date from 1979 to the date of record collection will add further records, although since these workers will be typically young and have had little time from first exposure to follow-up, few additional lung cancer cases are expected. Hence, the power calculations as supplied will be minimally affected.)

Hattis

Comment: "P. 19, Without more detail in the exact data used, it is difficult to critically evaluate the power calculations. Nevertheless, it is entirely credible that this study with so large a number of workers with likely much higher exposure that [sic] groups previously studied, will have good power."

Frank

Comment: "Given the findings in several other studies of diesel exposed populations, the assumption that there will be a two-fold increase in lung cancer among these miners may be overly optimistic."

Response: The issue of the power of the study is discussed at length on p. 9. It is important to understand that the size of the cohort study is subordinate to the case-control study, in that the cohort study had to be large enough to identify sufficient cases for the case-control study. For this reason, the power of the cohort study is not a major consideration, though it certainly is very adequate for the question it attempts to answer. We will add some additional material to the protocol to explore the power for lower potential risk.

SECTION 6 - THE NESTED CASE-CONTROL STUDY

Power considerations

Frank — Comment: "Given the findings in several other studies of diesel exposed populations, the assumption that there will be a two-fold increase in lung cancer among these miners may be overly optimistic. This is especially true if the control population will be other miners, rather than individuals from the general population."

Howard — Comment: "Section 6.E. -- Case-Control Study: The statement is made that the proposed cohort will yield a minimum of 180 lung cancer deaths based on an assumed OR of 2.0 associated with diesel exhaust exposure. What is the implication to the overall power of the study if substantially fewer cases are demonstrated?"

Moure — Comment: "The power of the study is enough to detect comfortably excess deaths for lung cancer if they were present."

Sokas — Comment: "My sole concern is that no modifications be made that would in any way reduce the power of the study design as proposed. This is particularly important for several reasons: First, the meta-analysis of prior studies attempting to identify a relationship between diesel exhaust and carcinoma as an outcome demonstrates that there is a problem with borderline statistical significance based on studies with low power. Secondly, the difficulty in accurately assessing smoking status that inevitably occurs with mortality studies will essentially increase the sample size needed beyond that which would otherwise be the case. Sample size is the single most important aspect of the study for this reason."

Response: The issue of power in the (case-control) study has been dealt with at length on p. 9 et seq.

Potential confounders

Cole/Corn/ Mandel — Comment: "...it is not obvious that supplementing interview derived data on smoking with data from other sources is appropriate. Care must be taken to achieve similar ascertainment of all information from the cases and controls to ensure valid comparisons."

Response: The primary purpose of the next of kin interview is to obtain

information on smoking. We plan to supplement the interview data with smoking data obtained from the 1976 cross-sectional survey and from company medical records, for both cases and controls.

Response rates

Cole/Corn/Mandel

Comment: "Cohort members may have died of lung cancer as many as 40 years ago. Thus, contact with their next of kin is problematic, and even for those contacted, there will be question about the reliability of the data. It would seem highly desirable to limit the case-control study to recent diagnoses of lung cancer. Systematic loss of early cases is acceptable, and may be of minor concern since an effect of diesel exposure may only occur after several years from first exposure."

Response: We, too, are concerned about locating next of kin of individuals who died on average 25 years ago. However, we believe the systematic loss of early cases to be unacceptable because it would tend to eliminate cases with shorter latent periods and potentially heavier exposures if the exposure decreased over time in some mines. It does not seem desirable to eliminate such workers from the study cohort. In particular, if diesel exhaust was a promoter of carcinogenesis, elimination of workers with shorter latent periods would decrease the ability to observe such an effect.

The rationale for elimination of early cases is the anticipated difficulty in contacting next of kin of subjects who died many years ago and the questionable reliability of information obtained from such next of kin. Two points merit consideration with regard to these concerns. First, subjects for whom we cannot contact a next of kin and supplemental smoking information is unavailable will be excluded from the case-control analysis. Second, although the reliability of smoking data from next of kin may decrease over time, the qualitative data we obtain should be adequate to control the effect of diesel exhaust for smoking.

Cole/Corn/Mandel

Comment: "The authors' goal of obtaining a 75% response rate may be difficult, especially if patients who died in the 1950s - 1970s are sought for enrollment..."

Response: Data from a previous NCI nested case-control study of lung cancer among pest control workers employed in 1965-69 indicated that 95% of the surrogate respondents were locatable and 83% were actually interviewed.[12] Our goal of achieving a 75% response rate from the next of kin interview seems reasonable. The plan to supplement the smoking data with information from other sources is intended to minimize the number of subjects with missing smoking histories due to nonresponse from the next of kin interview.

Lung cancer as a contributing cause of death

Cole/Corn/Mandel

Comment: "There is no objection to using decedents with lung cancer as a "contributing cause". However, there will be few, or no such persons. The words "due to" are inappropriate if a contributing cause is referred to."

Response: We agree. Section 6.B.1 will be changed to read "Cases from each mine will be all lung cancer deaths (ICD-O = 162) as specified ..."

Interviews of next of kin

Cole/Corn/Mandel

Comment: "How will the study be blinded from the interviewers? What about the respondents? What will they be told regarding the purpose of the study?"

Response: Interviewers will not be told that all the cases are deceased so they will not know that all direct interviews are with controls. Neither the interviewers nor the respondents will be told the case/control status. Subjects will be told that the purpose of the study is to learn about how environmental factors, such as smoking, affect health. The following will be added to section 6.C.2: "Every effort will be made to blind the interviewers with regard to case/control status and diesel exhaust exposure. Interviewers will not be informed that all cases are dead and some controls are living. Thus, they will be unable to surmise that if an interview is conducted directly with a respondent, it must be that of a control."

Frank

Comment: "A potential serious flaw in this study is the use of surrogates to report cigarette smoking history. The scientific literature is replete with studies on the use of surrogates, and almost universally there are flaws in this approach, with a significant amount of under reporting. For other proposed aspects of the study, such as dietary history, this becomes most inappropriate. Even contemporaneous dietary history among active workers has considerable difficulty, and retrospective data is not especially accurate."

Response: On the contrary, the scientific literature is replete with studies showing that next of kin, particularly spouses, provide reliable data regarding cigarette smoking.[13,14] With regard to dietary factors, only a few basic questions on fruit and vegetable consumption, which has been shown to be protective for lung cancer, will be included in the questionnaire. Most next of kin in this study will be wives, and wives have been found to provide reasonably good dietary histories for their husbands, particularly for broad categorical data.[15]

Hattis

Comment: "The protocol for the case-control study should be modified slightly to allow ascertainment of the effects of the information source on the assessment of confounders and effect modifiers. The current plan calls for interviews of next of kin for the lung cancer cases, but direct interviews of the "control" workers themselves for those who are still alive. This creates a difference in information source between cases and controls that could complicate the interpretation of the interview data."

Eisen

Comment: "In addition to the proposed matching factors, however, controls should also be matched on vital status at the time of interview in order to reduce differential recall bias. That way, the quality of interview data will be the same for both cases and controls."

Response: The interview in this study is designed primarily to obtain information on confounders. In this situation, there is no literature to support the notion that matching on type of interview will result in comparability of information from cases and controls.[16-18] In fact, conducting an interview with the next of kin of a living subject is not comparable to conducting an interview with the next of kin of a dead subject. Taking all factors into account, we believe it is preferable to obtain the most accurate information possible for both cases and controls.

Cole/Corn/Mandel may asbestos

Comment: "The authors ... downplay the potential for information bias, which be especially problematic for questionnaire items such as medical history, exposure, and several other factors which next of kin may not be familiar with as are the workers themselves."

Response: The main thrust of the interview is to obtain information on cigarette smoking, the major potential confounder in this study. In our opinion, misclassification of minor confounders, such as medical conditions, that are of low prevalence and/or are weak risk factors for lung cancer, will not threaten the scientific validity of this study.

Cole/Corn/Mandel

Comment: "All the cases will be deceased and some will have died many years ago. It is likely that many spouses and siblings may also be deceased. The investigators should provide justification for relying on 'close relatives' or 'children' for historical information, particularly in view of the fact that many, and perhaps most, controls will be interviewed directly."

Response: This cohort is relatively young. The average age in 1995 was 54 years old. Thus, we are expecting that most of the spouses (almost entirely wives in this study) will be alive at the time of the interview.

Use of telephone interviews

Cole/Corn/Mandel

Comment: "The investigators should justify the use of telephone interviews given the magnitude and cost of the study."

Response: The determining factor in the decision not to conduct in-person interviews in this study was the length of the interview. Because the primary purpose of the next of kin interview is to obtain information on potential confounders, the interview will be relatively short. The added expense of conducting in-person interviews in this study seems unwarranted.

Pathology slide analysis

Davis

Comment: "P.22. It is unclear why investigators will obtain pathology information. Is it solely for descriptive purposes or will the study be limited to pathologically confirmed cases? The Massachusetts experience suggests that autopsy records will be available for relatively few lung cancer cases. Hospitals

may or may not have pathology records. Availability may vary by age at death (older people more likely to die in nursing homes without pathological tests); and by calendar time (changes in health care environment may change likelihood of accessing pathology records.) Investigators should clarify why they want these records. If necessary, the investigators should explore possibility of accessing state tumor registry information. New Mexico and Wyoming, for example, have had tumor registries since 1969 and 1967, respectively."

Dement

Comment: "Page 22. Pathology: The proposed case ascertainment and analyses of the pathological slides needs further development. How will this [sic] data be analyzed and used? As this portion of the study is currently written, only descriptive data concerning the lung cancer cell types will be collected. This likely will be of very limited value in that most lung carcinogens are not very specific concerning cell type."

Response: The following will be added to section 6.B.1: "The purpose of the slide review is to confirm the diagnosis of lung cancer as well as the histologic subtype. For cases with no slides, pathology reports will be considered acceptable confirmation of diagnosis. Cases that are found either not likely to be carcinoma of the lung or metastatic to the lung by slide review or pathology report will be excluded from analysis. Cases with no slides or pathology report (i.e., clinically diagnosed cases) will be included in the analysis. If the proportion of cases with usable slides is high, histologic subtype-specific analyses will be considered.

Hattis

Comment: "P 20, par 1. Also, as previously mentioned, I think measures of internal accumulated dust should be added here, based on saturable particle clearance models where indicated, incorporating the effects of smoking."

Response: We will explore the feasibility of incorporating measures of internal accumulated dust into the tissue specimen component.

Dement

Comment: "The oncogene/suppressor gene part of the proposal is not developed. No information is provided concerning what analyses will be done and by whom. How will these data be interpreted?"

Dement

Comment: "The pathological part of the study includes no control group. This severely limits interpretation and use of any data obtained. For example, a properly designed pathological study could possibly be used to address some confounders such as asbestos and silica. One possibility would be to use the NIOSH/CAP fibrosis grading scheme for lung tissues in order to address the significance of silica and asbestos exposures among study miners compared to a properly chosen control population."

Response: The following will be added to section 6.B.1 of the protocol: "If pathologic samples are available from an adequate number of diesel exhaust exposed cases, consideration will be given to identifying a series of lung cancer cases without diesel exposure, matched to exposed cases on hospital, smoking

history, age, gender, and race. This will allow a comparison of tumor characteristics at the molecular level (e.g., oncogene and tumor suppressor gene mutations) between these two groups. A more detailed protocol will be developed if an adequate number of archived tumor samples can be retrieved from deceased cases.

Hattis

Comment: "P. 22, For the reasons outlined earlier, I am very happy to see the paraffin blocks of tissue requested. These could prove invaluable for future tumor molecular pathology and (if normal tissue is included) somatic mutation assays."

Response: We concur with these comments.

Selection of controls

Gibbs

Comment: "Control selection should take into account: 1) regular use of respirators, whether or not use was mandated; 2) exposure to any other non-absorbable dust in the submicron range; 3) employment above ground or underground."

Response: Information on respirator use is expected of doubtful utility. It will be considered during the exposure assessment and analysis phases of the study, and in interpretation of the findings. The significance of exposures to other non-absorbable dust in the submicron range will be assessed during the exposure assessment phase and data analysis. Information on work above ground or underground will be used in deriving worker exposures. None of the three has a direct bearing on control selection procedures.

Cole/Corn/Mandel

Comment: "Four controls per case is inefficient. It may be preferable to make no commitment to any selection ratio until preliminary results indicate how many cases there will be. Power per subject, and usually power per dollar, are optimized with a selection ratio of one. At 98 percent power, the proposed study may be larger than need be."

Eisen

Comment: "The control to case ratio of 4:1 ratio has been shown to be optimal in terms of power and costs."

Response: The allocation ratio is being revised to 3:1. When enumeration of the cohort by mine, gender, race/ethnicity, and age is complete, we will evaluate the feasibility of our plan for control selection and revise it if necessary (see section 6.B.2). A justification for the study power is given on p. 9. There we argue that the study power may well be less than the stated value given in the protocol. If it is less, the optimal strategy is not 1:1, because fewer controls per case would mean a need for more cases for equivalent power. This would require further mines to be included in the study, which is considerably more expensive than interviewing more controls from fewer mines.

Dement

Comment: "Page 22. Case-control Study: It is not entirely clear that incidence-

density matching will be used to select controls; however, this may be the case based on the description of procedures to be used. Incidence density matching should be used if it is not already planned."

Response: Incidence density matching will be used. The protocol will be modified to make this clear.

Davis

Comment: "P.22. What is the ethnic distribution of the workforce in selected mines? Will there be sufficient ethnic variability to select 4 controls per case matched on ethnicity?"

Response: Although we do not know the ethnic distribution of the study cohort, we do expect some Hispanics. Since Hispanics have a lower risk of lung cancer than whites, it will be efficient to match on ethnicity. If there is not sufficient ethnic variability to select 3 controls per case matched on ethnicity, we will revise our plan for control selection.

Case-control questionnaire

Dement

Comment: "Page 23. Case-control questionnaire: The questionnaire should collect information concerning time dependent variables where possible. For example, in the regression models, cases are compared with controls based on exposure variables at the time of death of index case (e.g., cumulative diesel exposure). Exposure to confounders also should consider this temporally. For example, smoking status of case and controls at the time of death of index case should be used in the models."

Response: We agree that timing of important confounders needs to be taken into account. In particular, with regard to smoking, we will obtain information on age started and history of quitting.

Other issues

Cole/Corn/Mandel

Comment: "Describe the 'special efforts' that will be made for hard-to-locate cases."

Response: For next of kin that prove difficult to locate, we will attempt to find them through such sources as the U.S. Postal Service, Motor Vehicle Registration Offices, Credit Bureaus and similar locator services.

SECTION 7 - THE BIOMARKER STUDY

Justification for the biomarker component

Cole/Corn/Mandel

Comment: "The biomarker study appears to be a study in pursuit of an explanation for a problem that is not known to exist. This study should be justified."

Frank

Comment: "The biomarker studies, while of some intrinsic scientific interest, are

not essential to answer the key point of this study. Such biomarker studies might well be done effectively and more inexpensively with an animal model."

Hattis — Comment: "The biomarker aspect of the project should be encouraged and if possible extended."

Moure — Comment: "The inclusion of a bio-marker study of 50 heavily exposed workers is a welcome addition to the design. This lateral study will be an important factor to illuminate the existence of mechanisms of tumor induction of nitrogenated Polycyclic Aromatic Hydrocarbons (N-PAH), as well as, direct evidence documentation of effect [sic] of DE exposure."

Landrigan — Comment: "The biomarker study is an innovative addition to the project. It may or may not add a great deal of science to the overall endeavor, but it is a worthwhile undertaking, and in the context of the overall study I would support it."

Rall — Oral comment: He said that the biomarker study is a good step.

Response: There is clearly a divergence of scientific opinion on the merits of the biomarker study, though more reviewers supported it than were against it. The study's primary goal (i.e., to obtain insight into the bioavailability and genotoxicity of nitro-PAH from diesel exhaust exposure) and secondary goal (i.e., to enhance exposure assessment for the cohort/case-control study) will be clarified. An interpretation of results from the biomarker study in the context of results from the cohort/case-control study will be provided. The importance of obtaining insight into the bioavailability and genotoxic potential of potential carcinogens, and the incorporation of this information into the evaluation of the carcinogenic potential of a particular exposure, has been recognized by IARC.[6.19]

Objectives

Hattis — Comment: "P. 22, bottom of page. I would also add a fourth objective here--to evaluate hypothesized synergism in dose between cigarette smoking and diesel derived particulate matter, because of the presumed slower clearance of diesel particulate in smokers."

Response: We note in the data analysis that we will evaluate the presence of interactions between cigarette smoking and diesel exhaust exposure for each biologic outcome.

Nitro-PAHs and carcinogenesis

Gibbs — Comment: "The introduction to the biomarker section references two potential mechanisms for a hypothesized carcinogenic effect of diesel particulate; however, the biomarker protocol is designed only to look for evidence to support a genotoxic mechanism (and a consequent zero threshold risk assessment

model).

A non-genotoxic 'lung overload' mechanism has been hypothesized by several authors to explain the carcinogenic effect of diesel, carbon black, titanium dioxide and other submicron particulate dusts observed in recent rat studies. If this mechanism were proven true, it would corroborate rat study data and support a risk assessment model with a no-effect threshold. If not substantiated, it would indicate that the rat studies may be irrelevant with regard to human cancer risk. The lung overload hypothesis could be tested by:

> A. Performing a second nested case control study comparing the pathology slides, identified in the first case control study with additional pathology slides identified from other lung cancer victims. Underground mining, diesel exposure, age, sex, smoking and other confounders could be controlled for. Endpoints would be pre-determined based upon review of pathology slides from recent rat studies that appear to show an association between diesel particulate exposure and lung cancer.
>
> B. Adding lung lavage tests to the biomarkers protocol to determine whether or not diesel exposed miners are 'lung overloaded'. It would be necessary to control for cigarette smoking as well as other submicron particulate."

Response: Review of the recent literature[20,21] suggests that particle overload is less likely to be relevant for humans . Further, direct evaluation of the presence of particle overload in humans involves either giving subjects a radio-labeled tracer to assess particle clearance or conducting pulmonary lavage. Neither of these approaches is warranted at this time given the lower likelihood that this is an important mechanism in humans. Such invasive studies would only be considered if the mortality studies are positive and the biomarker findings are negative. We previously noted that we would attempt to collect pathologic samples from cases for molecular analyses. If an adequate number of samples can be collected from cases, we will consider adding to the protocol collection of samples from a series of lung cancer cases unexposed to diesel exhaust for comparison.

Biological samples

Dement

Comment: "The rationale behind the protocol for collection of samples is not adequately described. For example, how were the various sampling times decided upon? What is the rationale for urine sample following a caffeine dose? What use will be made of the pre-work week and pre-shift samples?"

Response: The urine sample after caffeine intake is used to measure the ratios of various caffeine metabolites in order to measure CYP1A2 and NAT2 phenotypes.[22] The purpose of pre-work week and pre-shift samples is to establish a baseline level for each biomarker which will reflect, for the most part, nonoccupational influences.

Data analysis

Hattis

Comment: "P. 24, next to last par. Caution should be exercised in transforming variables for specific purposes. For purposes of statistical testing of differences between groups, a normalizing transformation is often needed. However, when quantitative models are being made of the relationships among variables, care should be taken that the shapes of relationships dictated by chemistry and physiology is not distorted. I have seen many a biostatistician take a relationship that should be linear at low doses (e.g. between an adduct level and an exposure level) and for statistical convenience do a logarithmic transformation of the data that destroys the linearity that can be inferred from physical principles. Where physics and convenience in regression modeling conflict, it is the convenience in regression modeling that should be sacrificed."

Response: The issue of transformations in statistical analysis is a recurring problem. Modern statistical methods (e.g., Generalized Linear Models) permit both the error structure (e.g., Normal distribution) and the form of the relationship (e.g., linear) to be specified, thus avoiding the distortion noted by Dr. Hattis.

Other biomarkers

Hattis

Comment: "P. 24, 2nd paragraph. I would add measures of the urinary elastin breakdown products, desmosine and isodesmosine."

Response: Urine will be put into long term storage in order to measure other relevant biomarkers, with attention to informed consent for future uses.

SECTION 8 - EXPOSURE ASSESSMENT

Zone based approach and associated topics

Cole/Corn/Mandel

Comment: Concern was expressed about the choice of a zone-based assessment approach to the retrospective exposure assessment, rather than job title, or group-based assessment.

Dement

Comment: "Statistical criteria for selection of homogeneous exposure zones (HEZ) are not defined. How many samples of each zone will be collected during the industrial hygiene studies at each mine?"

"While the HEZ concept is very useful and appropriate for this study, the possibility of higher exposures for some workers within such zones due to their jobs (ie., diesel equipment operators) should be considered. Personal sampling of such workers should be considered. Personal sampling of such workers during the surveys is recommended. Are the MSHA 1976 samples useful in this regard?"

Frumin

Comment: "Second, the Exposure Assessment Protocol is in need of additional work, along the lines already suggested by the Task Force which made relevant

recommendations in 1996. NIOSH/NCI should incorporate those recommendations."

Tuggle

Comment: "In regard to the revised Exposure Assessment Protocol of 1996, we believe it should be applied to the 1995 draft document. In short, all parties to the 1996 Exposure Assessment Task Force stands [sic] in full support of the revised protocol and submits it as an excellent model."

Spear

Comment: "My concerns relate to the proposed intent of using area samples in the context of homogeneous exposure zones and the relationship of data so obtained to personal exposure measurements. I doubt that anything approaching a homogeneous exposure zone exists in this environment and if [sic] is well established that the relation between area and personal samples in many settings is often ambiguous at best, particularly where there is near field exposure.

"I would recommend that the prospective exposure assessment utilize the analysis of variance model that Rappaport, Paul Hewett and others have worked with and apply that idea to the characterization of exposures within the various job classes. This would link more directly to the historical data which, I presume, is mostly survey or compliance monitoring data based on personal samples. If there is historical area monitoring data it might be possible to use it to adjust the means of the personal exposure models or do this via the indirect data you hope to collect. I suspect that one might make a case that the within- person and between-person variances could be assumed constant over time for a given job class.

"I note that the prospective exposure study, being conducted as it is over a number a [sic] mines, could also assist in the construction of a regression model to relate personal (and area) data to the various indirect variables you might use in the historical reconstructions."

Moure

Comment: "The inherent obstacles of imprecision of historical reconstruction of exposures are being appreciated by the researchers and can be measured by the methods described. The NCI and NIOSH researchers have a good track record measured by the methods described. The NCI and NIOSH researchers strategies to quantify historical exposure to Acrylonitrile in the chemical industry attest to the abilities of the research team to accomplish the historical exposure assessment task. The methodology of assigning lifetime exposures by combining current and historical data would never be perfect. However, the research team's strategy described in the protocol is a very credible state of the art method that will provide a rational approach to a dose-effect relationship between DE exhaust and health effects."

Response: We concur with the reviewers who suggested a mine/department/job title approach. A zone-based approach was suggested in the 1995 version of the protocol based on the selected sample of work histories from one mine. After we had reviewed detailed information on the work histories from all of the selected mines in the feasibility study, we decided that the mine/department/job title combination approach would be a better method to capture the between-job

variability in exposure levels. The mine/department/job title combination approach will be implemented in the revised protocol. This is a standard method, which has been used in many published epidemiologic studies.

Cole/Corn/Mandel — Comment: They noted that details of the method of time-motion pattern assessment study are not presented.

Response: The time-motion assessment study was an essential part of the zone-based exposure assessment approach. Because the retrospective exposure assessment method will be based on mine/department/job title combination, a time-motion evaluation study will not be a part of the new exposure assessment method.

Use of area samples

Cole/Corn/Mandel — Comment: There was concern about the 'use of area samples in representing personal exposures,' and the 'use of historical personal and area samples in the assessment of exposure.'

Hall — Comment: "The industrial hygiene scientific literature clearly demonstrates area concentrations are poor predictors of personal or occupational exposure."

Response: Under our modified strategy, area samples are not going to be used directly in estimating the personal exposure if personal measurements are available. The area samples of direct surrogates will be collected from each study department and the results will be used in the mine-specific correlation studies. In addition to the correlation studies, both current and historical area samples will be used in estimating exposure levels for each study department defined in the protocol. The results of both current and historical personal samples will be used in estimating exposure levels for unique mine/department/job title/calendar period combinations. In some circumstances area samples may be all that are available. Area samples are clearly better than no samples.

Correlation studies

Hattis — Comment: "P. 29, Section 8.C.3.c. I assume that in addition to correlation coefficients, the authors will develop predictive regression models that will be used to estimate absolute values of the different primary diesel exposure surrogates. Only such absolute value models of particular measurable exposures (and the associated risks) will give diesel design engineers, OSHA and MSHA the control parameters they will need for later consideration of practical control measures."

Response: "Correlation" in this instance means the derivation of relationships between elemental carbon (and other) exposures for use in assessing retrospective exposures using historical data.

Exposure variable terminology

Cole/Corn/Mandel

Comment: Concerns were expressed about some terminology used in the protocol, such as "elemental carbon, rather than diesel particulate," "Homogeneous Exposure Zone," "priority index," and "baseline estimates."

Response: In the new protocol, we will be identifying three surrogates (i.e., elemental carbon (EC), submicron particulate (SP), and submicron combustible dust (SCD)) to represent diesel particulate.

1976 surveys

Howard

Comment: "Section 8.C.6.a. -- Collection of Historical Monitoring Data for Direct Surrogates of Diesel Exposure: Studies of mine environments conducted by MESA is [sic] mentioned. Should more information be given on what was done during these studies and were the results of these studies ever correlated with health effects as discussed? If so, what was the size of the population that was studied and what was the age distribution and duration of exposure of the population? Didn't NIOSH do a study of nonmetal mines to look for adverse effects from exposure to diesel emissions? If so, what was the size of the cohort they studied?"

Response: Industrial hygiene details of these surveys are available in a report which will be attached as an appendix to the revised protocol. In response to the questions about the health effects study, we would note that NIOSH undertook a morbidity study in 21 metal and non-metal mines. The total study consisted of about 5,000 miners whose mean age was close to 40 at time of examination. A separate analysis of data from the potash mines component of the study was also completed.[23]

Confounder estimation

Dement

Comment: "The exposure estimation method for quantitative exposures apparently applies only to diesel pollutants--not confounders such as silica and radon. If exposures to confounders are highly correlated with diesel exposures, it may not be possible to estimate the separate effects of each exposure. Some effort needs to be made to address this issue at the outset. Hopefully, given the number of different mines and job titles to be studied, natural gradients will emerge which allow separation."

Weeks

Comment: "One aspect of exposure that may be missing is assessing exposure of surface miners to crystalline silica, a possible lung carcinogen. If surface miners are included in the control group, their exposure to silica should be assessed. Surface drill operators and bull-dozer operators are occupations that have seen high exposure, above the NIOSH REL and PELs of OSHA, MSHA-Coal and MSHA-Metal/Non-metal."

Response: The mines in this study were selected because all evidence shows that they have low levels of confounding variables. Hence, we feel that confounding is unlikely to be a problem. We will be sampling for confounders as a check that our assumption is correct. If events prove us wrong, we will evaluate the most

appropriate course of action. One method may be to omit workers with the higher exposures to the confounders, if such exposures are confined to a small group of individuals, and if doing so does not remove those workers with high diesel exposure. We may also be forced to undertake further sampling for the confounding variables in order to quantify exposures. Alternatively, we may find it possible to account for confounding exposures adequately through use of dummy variables based on some categorization of workers according to level of confounding variable. The actual choice of strategy will clearly depend on circumstances as we find them.

Choice of exposure indices

Moure

Comment: "The proposed agents to be quantified for measurement of DE are a combination of well studied components of DE (Sub-micrometer particulate, respirable particulate, total particulate, N-PAH, CO, CO2, NO and NO2). The most traditional measurements, specially [sic] particulates, could have a substantial historical data base. In addition, other state of the art surrogate [sic] of DE exposure are being measured (elemental carbon) that together with sub-micron particulate and sub-micrometer combustible dust will provide a very good description of current exposures. This in combination with the most traditional components of DE will permit the assessment of past and current exposures."

Response: We concur with this evaluation. The exposure indices chosen reflect a range from traditional to new, state-of-the-art.

Weeks

Comment: "Exposure assessment is the most critical aspect of this study. Given the apparently high level of exposure, the range of exposure, and historical data, this is a rich source of data. The two key goals of exposure assessment are accurate assessment and linking each member of the cohort with these assessments. Appropriately, a job-exposure matrix combined with employment histories is intended to accomplish these two tasks: assessment and linkage.

"It is also important to define carefully exactly what aspects of exposure are being measured. Diesel exhaust, as noted, is a complex mixture of both respirable particulate matter and gas-phase ingredients. Most prior studies have measured exposure to particulate matter as a respirable mass. In order to complement prior studies, whatever measures of diesel particulate are made (such as of elemental carbon), they should be convertible to respirable mass. It may be that there are better ways (i.e., more closely related to the occurrence of lung cancer) of measuring exposure to particulate matter but unless these measurement methods are convertible, we will not know.

"Gas phase ingredients are important to measure as well, not only for the intrinsic value of evaluating their effects but also for their utility as surrogates in estimating exposure to diesel particulate (or other ingredients) when direct measurements are lacking. Their intrinsic value is that they may play some sort of interactive role in lung carcinogenesis. Though these studies are not designed to evaluate such interactions, it is possible that some findings may suggest additional inquiry into

interactive effects.

Response: Our correlation studies, in which side-by-side sampling of different exposure variables will be undertaken, should provide information relevant to this request. We also know of other ongoing studies that are specifically designed to answer this question. We will be staying in contact with these researchers so as to be as knowledgeable as possible on this issue.

Dement — Comment: "Several surrogate measures for diesel exposures are proposed. Mine ventilation parameters may vary greatly over short periods of time, therefore, averaging parameters over longer periods of time may be needed."

Response: This aspect will be evaluated when we assess and summarize the surrogate information.

Sampling for elemental carbon

Hall — Comment: "What is the rationale behind using elemental carbon as the prime surrogate for diesel exhaust particulate.?"

Response: Elemental carbon is not being proposed as the "prime surrogate for diesel exhaust particulate". In fact, we are proposing three analytes as surrogates for diesel exhaust exposures. They are elemental carbon, submicrometer particulate, and submicrometer combustible dust. Historical intensity levels will be estimated for each of these surrogates using the results of the current monitoring survey and the available historical information on other surrogates of diesel exposure. However, we believe that elemental carbon is an appropriate diesel exhaust surrogate because there are no sources of elemental carbon in the selected mines except for diesel exhaust particulate. This removes any confounding effect caused by smoking or oil mists. Additionally, NIOSH has developed an analytical method for the measurement and analysis of elemental carbon and it is the recommended method of HEI. This method is becoming more widely used and accepted, but we have elected to use other surrogates as well, partially because of the reluctance of some investigators to recognize the potential of this method.

Hall — Comment: "There is also the concern of interference occurring from the presence of mine dust."

Howard — Comment: "Finally, we offer one comment regarding the January 14 Board of Scientific Counselors meeting. During a presentation to the Board, the Methane Awareness Group indicated that there were problems with diesel particulate sampling methods. Specifically, Dr. Thomas Hall stated that there were problems with elemental carbon (EC) measurements in trona mines, and that the relationship of EC to other measurement techniques had not been adequately established.

"This has not been MSHA'S experience. For analysis of elemental carbon samples collected in trona mines, there is a clear separation between the peaks on the

thermogram representing the bicarbonate and the elemental carbon. This information had been previously shared with Dr. Hall. While there is some variability in the relationship of elemental carbon to other diesel particulate measurement methods, MSHA samples show a much narrower range than indicated by Dr. Hall. Additionally, as part of the exposure assessment, the relationship of elemental carbon to other sampling methods will be evaluated in each mine."

Response: Trona does not cause an interference in the analytical method. The peak resulting from the trona dust is completely separated from the pure elemental carbon peak. We are in agreement with Mr. Howard from MSHA on this issue.

Accuracy and reliability of exposures

Gibbs

Comments: "In the event that a lung cancer association is shown with diesel particulate exposure, an accurate historical assessment of exposures will be an essential factor in determining a 'safe' exposure limit. Historical exposure assessment must include:
a) a determination of when and if the use of low sulfur fuel was implemented;
b) a determination of when and if the use of diesel exhaust control technology was implemented;
c) the historical use of personal protective equipment (not just whether or not it was mandated)."

Response: The accuracy of the historical exposure estimates is crucial not just in determining a "safe" exposure limit, but also to obtain a scientifically valid exposure-response relationship. We will examine the historical information on the use of low sulfur-containing fuel, diesel exhaust control technology and personal protective equipment, when available.

Cole/Corn/Mandel

Comments: "It is very complex to extrapolate today's results from earlier time because diesel engines and fuels are very different today from even five years ago. How will these technological improvements in engines/fuels be incorporated into modeling of emissions?"

Spear

Comments: "On another theme, I am concerned with the possibility that the organics adsorbed onto the particulate matter may play an important role if diesel exhaust is found to be carcinogenic in humans. It seems very likely that the composition of these organics has changed markedly over the years as the engine designs and operating conditions have changed. Hence, the carcinogenic potential might be only weakly linked with the particulate carbon dose. While there is little that can be done to investigate this historically, I think it should be a subject of investigation in the context of the biomarkers study. I am not enough of a chemist to know how to sensibly fractionate the organics that can be desorbed from the collected exhaust but, assuming their [sic] is some sensible approach, any insight into the variability of these fractions and their correlation structure in various settings would be enlightening."

Response: We are aware of the fact that technological improvements in engines, fuels, exhaust systems, and control measures have impacts on the level of diesel exhaust exposure. We will emphasize collection of the historical exposure information on changes of engine types, fuel type, exhaust type, and control measures at each mine/department combination. Measurement values for the other surrogates before and after the specific change will give us an understanding of the effects of these technological improvements on the diesel exposure levels. We will also have an opportunity to measure the impacts of these improvements directly in our current IH-surveys using the different types of old and new equipment, high and low sulfur-containing fuels, and old and new exhaust and ventilation systems in different study mines. Having both current and historical information on these technological improvements will help us to do more accurate extrapolation from current levels of diesel exposure to historical levels.

Hattis

Comment: "In order to make a credible estimate of true dose response relationships, it is vital not only to quantitatively estimate exposures but to estimate the uncertainties in the individual exposure estimates, both for the cohort and case control studies."

Hattis

Comment: "P. 25, last par. The absence of historical measurements of the primary diesel surrogates makes the kind of exposure uncertainty/variability analysis I outlined earlier even more essential."

Response: We agree totally that assessment of the intrinsic variability of the exposure estimates is a critical part of the study analysis. Not only does this information provide information on the overall reliability of the study, it also permits us to estimate the extent to which the results may be biased (attenuated) by random variability. As noted above, we intend also to look at the sensitivity of the overall findings to changes in the underlying assumptions in the exposure derivation.

Hall

Comment: "The primary and theoretical hurdle that must be overcome is the complete absence of personal exposure estimates for any measure of diesel exhaust particulate, or for that matter, the almost complete absence of any personal exposure estimates for any primary or secondary surrogate during more than 90% of the study period."

Response: While we do not seek to minimize the difficulty of the task of estimating valid exposures, the situation is not as bleak as is painted. If environmental conditions are stationary (that is, no major changes were made to ventilation, use of diesels, and work practices), one would expect that exposure levels would be likewise constant. Hence, it is not the time period that is of relevance, but the number of times there were significant changes to factors having major influence on exposure levels. Based on our existing information, we feel that the environmental situation changed in well-identified steps, and that reasonable actions can be taken to account for those changes.

Hall

Comment: "The use of personal exposure estimates for [sic] the MIDAS database

presents another problem."

Response: We are well aware of the potential problems associated with using data collected for compliance purposes in epidemiologic studies. Clearly, the data will have to be carefully evaluated. Even if the information is considered inappropriate for use in estimating exposures directly, it will probably have other applications, such as in determining relative trends in levels.

Hall

Comment: "This methodology will result in overestimation of individual exposures and add to the uncertainty of the proposed dose-response estimation process. In this study, the NIOSH/NCI research team has proposed using the mean exposure (a point estimate with no confidence bounds) to estimate individual exposures. Typically, exposure or concentration distributions in occupational settings are assumed to be log normal. This methodology can result in a severe overestimation of exposure."

Response: We disagree completely with this assessment. As noted by Armstrong, "...the arithmetic mean is also a relevant summary of the distribution of shift TWA exposures over a random sample of workers with the same job title."[24] In some circumstances, use of the geometric mean might be valid, but its use needs to be rigorously justified in terms of the exposure-response model that is being studied. An interesting discussion of the use of geometric versus arithmetic means is provided by Seixas.[25]

Hall

Comment: "The proposed study states that duplicate area samples will be collected during at least three production shifts during which normal mining operations are observed for underground operations and two normal shifts for surface operations." He goes on to say that the number of samples is too few for reliable estimates of zonal concentrations.

Response: In part, this question relates to the zonal approach, which is now superseded by the job-exposure matrix approach. However, it is important to note that the objective of the sampling is primarily for the purpose of establishing relationships between the new and older exposure variables. We will increase the number of samples, as suggested.

Other exposure issues

Dement

Comment: "Page 34. Historical exposure [sic] with a GSD 5.0 or less are [sic] to be used for baseline estimates. How was this criteria [sic] established?"

Response: This criterion was established based on work done by Emeritus Professor Robert Harris from UNC, a member of NCI's site visit committee (external peer review committee which oversees the work of the Cancer Epidemiology Branch). He has suggested that a GSD of 5 or less indicates a more stable mean value on which to establish the baseline value.

Hall

Comment: "The estimation of baseline exposures is unsupported by the proposed methodology." He goes on to say that the approach is poorly defined and that there is no reason to believe that mine conditions that exist today have any definable relationship with historical mine conditions.

Response: We disagree with this point of view. The basic mine processes have remained virtually unchanged in the mines for many years. We will be identifying factors that impinge on changes in conditions and adjusting exposures appropriately, based on input from individuals knowledgeable about the specific mining environment being studied.

Dement

Comment: "It is not clear how standardization of job codes will be accomplished for the entire study. It would seem important that a first level analysis be done according to similar groups of jobs across the mines. This would require that a more uniform coding scheme be developed. At a minimum, it should be possible to collapse mine specific job categories into comparable groups across mines."

Response: Under the revised exposure assessment approach to be described in the revised protocol, the emphasis will be on jobs rather than zones. In this new approach, we expect to find jobs which are similar with regard to diesel exposure levels, and which can be collapsed into larger strata. For some jobs, it may well be possible to collapse across mines.

Need for further detail

Hall

Comment: "There is a need for greater specificity in the proposed methodology if the proposed exposure assessment is to provide the occupational time-weighted average working life exposures describes [sic] as essential to developing a dose-response curve for the anticipated disease in the miner population."

Response: The modified protocol and its appendices will provide extensive detail on the proposed methods.

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A Summary of Responses from the Second Peer Review Meeting Concerning the Study Entitled

"A Cohort Mortality Study with a Nested Case-Control Study of Lung Cancer and Diesel Exhaust among Non-metal Miners"

held at the meeting of the NIOSH Board of Scientific Counselors on April 30, 1997 in Washington, DC

June 20, 1997

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Introduction

The following points were raised or discussed at the second Peer Review meeting concerning this project held on April 30, 1997. This document summarizes the issues and provides our response.

General comments

Shorten duration of study (2- 4 years suggested).

> We have considered various options for accelerating the mortality components of the study. These include strategies to speed up data processing and options to curtail mine surveys if it appears that sufficient cases will be obtained for the case-control study. Although we plan to adopt these, our experience to date with data entry from the feasibility study and with mortality follow-up for other studies indicates that three years is the minimum time for completion of the cohort study follow-up. (Note that the decision to expand the inclusion period up to 12-31-1996 has added to the data entry burden.)
>
> As a further step to enable the study results to be disseminated more expeditiously, we have decided to undertake the principal analyses in two stages. The Phase I analysis, which will take place in year 4 will comprise an analysis of the cohort data using indirect surrogates of diesel exhaust exposure (e.g., tenure and job). We will also undertake a semi-quantitative exposure-response analysis of the case-control data concurrently. Both analyses will take advantage of the IH data available at the time. Results from Phase I should become available towards the end of year 5. The Phase II analysis of the cohort and case-control data, which will employ quantitative exposure assessments for individuals, will take place in year 5, with dissemination of results in year 6.
>
> (It should be noted that completion of Phase I of the cohort study to the extent noted above is independent of any other component of the overall study. In particular, it is not dependent on derivation of personal exposures for the workers. The cohort study cannot be completed any faster by eliminating or curtailing other aspects of the overall study. It is also important to note that the time line represents the best-case scenario. Unforeseen occurrences unrelated to the scientific aspects of the study could cause delays in the projected completion dates.)
>
> A time-line for the major activities of the study is given on p.17 of the revised protocol.

Provide further information on mine selection procedures.

> Appendix B of the revised protocol provides more information on the mine selection procedures for the study.

Provide further information on power of the study.

Details on power for the cohort and case-control studies have been removed from those sections and are now included in Section 4 of the protocol. Additional material has been added to enhance the discussion of study power. The decision was made to base the study size on detecting a doubling of lung cancer risk among the *high* exposed group in the case-control study. This is a change from the original protocol in response to review comments, in which the power calculation was based on a doubling of risk *overall* (i.e., both high and low/moderate exposed) diesel exposed workers. This results in a power of about 80% for a 4:1 matching.

Use fewer mines (4 suggested).

We have pursued this idea by considering power estimates and can find no basis for reducing the cohort to four mines. The power of the case-control study based on lung cancer cases from the four largest mines in the set of 10 original primary mines is about 66%. This it too low for adequate study. It also happens that these larger mines tend to have lower diesel exhaust exposures overall, which has undesirable ramifications for detection of exposure-response. As noted above it may be possible to employ fewer than 10 mines, if those visited initially supply sufficient lung cancer cases.

Smoking data from medical records may cause bias.

We concur with the reservations expressed concerning potential bias associated with smoking data from medical records. However, we are hesitant to abandon this source of information entirely. Instead, we feel we should collect this information, but carefuly evaluate it. This evaluation will include analysis of the data with and without its incorporation in the assessments of smoking.

Provide information on how the distribution of workers across exposure groups was determined.

Some information pertinent to this question can be found in Table A.1 of the protocol, which provides information on the percentage of workers underground for all 24 feasibility study mines. This information suggested that about 40% of the workers worked underground, and were thus exposed to diesel exhaust. Our knowledge of the mining processes in general indicated that another 10% of the mine work force would be exposed on the surface, making 50% exposed overall. We believe that this exposed group can be divided about equally into high and low/moderate exposed groups. We have clarified this point in the revised protocol.

Cohort study

Define what causes of death (other than lung cancer) will be analyzed, and how the findings will be interpreted. Indicate the likely power of these analyses.

Page 20 of the revised protocol delineates causes of death to be examined *a priori* based on scrutiny of the published literature on mortality and exposure to diesel exhaust. Other causes will be examined, and positive findings treated as hypothesis generating. We cannot easily address the issue of power for each individual cause, though it is assumed that there will be adequate power for elevations in causes of death which occur about as frequently as lung cancer and for which any risk associated with diesel exhaust exposure is as great as that assumed for lung cancer in the power calculations.

Include labor union records as a means to ascertain vital status.

We have now included this step in the methods (see p. 20).

Case-control study

Analyze pathologic samples for potential confounders, e.g., asbestos fibers, silica.

The protocol has been changed to reflect an interest in pursuing this concept, given that sufficient material can be acquired for valid analysis.

Do personal rather than telephone interviews.

Current evidence indicates that telephone interviews are as valid as face-to-face interviews. Studies have found that there are few differences in the statistics elicted in one mode versus the other.[1] It seems likely, for the collection of such information as smoking, which should be known with a good deal of certainty by next of kin, that telephone interviews should be as reliable as face-to-face interviews..

Retain 4:1 matching ratio.

Based on the comments received at the last (April 30) BSC meeting, we have decided not to change to a 3:1 matching (as proposed in our responses to the initial BSC review comments - document dated April 3, 1997), but to retain the 4:1 matching ratio. The 4:1 ratio is needed to provide sufficient power in order to detect a doubling of risk in the high exposure group.

Use only more recent decedents, i.e., those dying after 1985.

The critical information we are eliciting from next-of-kin pertains to history of smoking. Next of kin have been found to accurately report on the most important aspect of the smoking history, i.e., the subject's smoking status. Restriction of the study to those dying after 1985 is not necessary, and is undesirable because it would would reduce the number of cases, and hence reduce the power of the study to an unacceptable level. To redress the loss in subjects, additional mines would have to be included in the study, leading to

greater cost and industry burden.

Consider effect of error in classification of confounders on assessment of the interaction between exposure and confounders.

The effect of misclassification of confounders in evaluation of the interaction between confounders and the exposure will, of course, depend on the magnitude of the misclassification. In the instance of cigarette smoking, this is not likely to be a serious bias because the accuracy of information on smoking status (ever/never) as determined from the next of kin has been shown to be excellent.

Biomarker study

Justify the biomarker study in terms of biological exploration, rather than its use as a predetermined mechanism for interpretation of the mortality data.

Changes have been made to the biomarker study section of the protocol to reflect these comments (see p. 24)

Exposure assessment

Be flexible with regards to estimation strategy. Allow room to employ a combination of homogeneous exposure zone/time-motion study with mine/dept/job combination as appropriate. Acknowledge potential for task based study in elucidating and assessing exposures.

The exposure assessment of the protocol has been modified to describe the utility and use of both job-based and zone-based IH assessments of exposure levels for development of personal worker exposures. Both methods are now an intrinsic part of the study protocol.

Confirm that a mine-based correlation strategy is planned.

This is stated in the protocol on p. 30.

Discuss issue and impact of blasting on diesel exposure assessment and describe how it will be dealt with.

NO_2 levels are expected to be an important direct historical surrogate for diesel exhaust exposure. Blasting also produces NO_2, and it therefore can pose a difficulty for the retrospective estimation of diesel exhaust exposures. Because each mine has had a different history and extent of blasting usage, it is impossible at this time to make a global statement describing the exact procedures for dealing with this problem. Each mine will have to be considered individually, and the extent of the problem assessed by examination of all relevant data for the mine. Inter-correlations and temporal trends for

different diesel exhaust surrogates, including NO_2 and surrogates not affected by blasting, will be evaluated for internal consistency. Adjustments will be made, as necessary, for any interfering effect of blasting on the retrospective exposure assessment.

Add material in appendices to protocol describing available data, both historical (primarily 1976 data) and on correlations.

Appendix F in the revised protocol provides information on the historical 1976 survey data for the selected mines. Appendix E gives information from the feasibility study IH survey undertaken at the one mine; this includes correlations between the various primary and other direct surrogate variables.

Discuss the issue of compliance data, and how to handle the potential problem of bias.

Our feeling is that compliance data can help rank locations relative to each other and over time, but they probably do not provide absolute levels for use in exposure estimation. Hence, although they will be useful in elucidating patterns of exposure across mines and jobs, reliance will have to be made on the main survey data (1976, current, and other similar data) for establishment of absolute levels.

Discuss the similarity between the feasibility mine and the other mines in the study.

Appendix F reports on the historical (1976 survey) data for the selected mines (including the feasibility mine #16). This enables a comparison to be made between the feasibility mine and the other mines.

Discuss precision of elemental carbon measurements.

Appendix D of the revised protocol discusses the precision of the elemental carbon method using data from various studies.

Show which mines were in the 1976 IH surveys, and discuss the implications of having or not having data from these surveys.

Appendix B of the revised protocol shows which mines have the extensive IH data collected in the surveys started around 1976. It shows that the presence of this information was an important weighting factor for selection of mines into the study. The six mines of top priority for inclusion all were in the 1976 study, while a seventh mine with 1976 data falls within the next priority group. One mine with 1976 IH data was excluded from the study because its diesel usage was extremely low.

Although we would have preferred to confine the study to those mines with 1976 IH data, this proved impossible because additional mines are probably necessary in order to

achieve the desired study power. (However, note that the proposed sequential approach to including mines into the study by priority order may possibly obviate the need for inclusion of additional mines if sufficient lung cancer cases are realized from the mines of highest priority.) Lack of 1976 data is certainly a disadvantage, as it provides less anchorage for exposure extrapolation. However, our criteria for ranking mines ensures that all mines included in the study will have at least one anchorage point (1976 or the present), and we expect most to have two anchorage points. (Some mines may have further anchorage points arising from some other IH studies, including NIOSH Health Hazard Investigations.)

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A COHORT MORTALITY STUDY WITH A NESTED CASE-CONTROL STUDY OF LUNG CANCER AND DIESEL EXHAUST AMONG NON-METAL MINERS

NCI/NIOSH INTERAGENCY PROJECT

September 16, 1997

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1. SUMMARY

Diesel exhaust is a commonly occurring airborne contaminant. Exposure to diesel exhaust is ubiquitous in cities and among those who commute regularly on highways. Occupational exposures are also common among transportation workers and operators of diesel-powered equipment. Some workers, such as those in mines that use diesel-powered equipment underground, may experience high levels of exposure to diesel exhaust.

Although diesel exhaust has been classified as a probable carcinogen by the International Agency for Research on Cancer, and as a potential carcinogen by the National Institute for Occupational Safety and Health, the risk of lung cancer in humans is still not well defined. In particular, although 30 or more studies have examined lung cancer risk and diesel exhaust exposure, few have employed quantitative exposure measurements of diesel exhaust directly in their analyses.

The proposed retrospective cohort mortality and nested case-control study of about 8,200 non-metal miners (184,000 person-years) will investigate risk of lung cancer in relation to quantitative measures of exposure to diesel exhaust. In addition, it will determine whether there is evidence of elevated mortality from other causes among diesel exhaust exposed miners. An extensive effort to characterize current and historical exposures to diesel exhaust and to develop estimates of personal exposures will be an intrinsic part of the study. Another component of the study will relate biomarkers of exposure and effect to level of diesel exhaust exposure.

A feasibility study undertaken jointly by the National Cancer Institute and the National Institute for Occupational Safety and Health gathered information on 24 non-metal mines in which diesel powered equipment was used underground. Non-metal mining was the industry selected for study because of the high levels of diesel exhaust exposure experienced by some non-metal miners in the absence of confounding by exposure to radon. Based on examination of industrial hygiene data, personnel records, historical data on worker exposures, and other information, the 24 mines were ranked. Summation of the expected numbers of lung cancer cases from those mines (based on the null hypothesis) showed that 10 mines should provide sufficient cases for the case-control study. A special industrial hygiene survey undertaken at one of the 10 mines indicated that diesel exhaust exposures in certain areas underground were 5 - 40 times higher than exposures reported to be experienced by railroad workers or truck drivers.

The mortality study cohort will comprise all non-office workers from the selected mines who were employed for at least one year during the period from the date of dieselization at the mine until the end of follow-up on December 31, 1996. This cohort will be followed using standard procedures for vital status, after which cause of death information will be obtained from death certificates. A standard mortality ratio analysis will be undertaken, overall and by level of diesel exhaust exposure. Account will be taken of gender, race, age at follow-up, calendar time, time from first exposure, and any previous employment in high risk occupations for lung cancer based on data available from personnel records. In addition, indirect adjustment for smoking will be done using the Axelson approach. Poisson regression and Cox proportional hazard modeling of mortality will be carried out using exposures derived from the exposure assessment phase of the project. It is planned to undertake the mortality analysis in two stages: a Phase I analysis based on indirect exposure surrogates, such as tenure and job, followed by a Phase II analysis employing quantitative exposure assessments. The cohort study has a power of over 90% to detect a trend in risk from 1 to 1.4 to 2.0 for surface workers (essentially not exposed to diesel exhaust occupationally), for workers with low/moderate exposure, and for those with high exposure, respectively, at the $\alpha = 5\%$ level.

The nested case-control study will be based on deaths from lung cancer ascertained during the follow-up stage of the cohort study. We expect to identify a minimum of 160 lung cancer deaths from the cohort study, assuming a trend in risk of lung cancer from 1 to 1.4 and to 2.0 with increasing exposure to diesel exhaust. Four controls will be selected for each case from among members of the cohort who were alive at the time that the case died, matching on mine, year of birth, gender, and race/ethnicity. Information on smoking (active and passive) and other potential confounders (e.g., employment in high-risk occupations for lung cancer, diet, and certain medical conditions) will be ascertained by interview of next-of-kin of deceased cases and controls and direct interview of living controls. This detailed subject-specific information will permit more accurate estimation of diesel exhaust exposure and better control for confounding in the case-control study. Conditional logistic regression will be used to determine risk of mortality from lung cancer for various measures of diesel exhaust exposure, including cumulative exposure and average intensity. Smoking and other potential confounders (as noted above), will be included in the model as deemed necessary. The role of smoking as an effect modifier of the relation between lung cancer mortality and diesel exhaust will be investigated, if numbers permit. As with the cohort study, a two-stage analytical approach will be adopted. Phase I will be based on relative exposure (i.e., a semi-quantitative) data, followed by a Phase II analysis based on quantitative exposure assessments. Assuming an overall odds ratio of 1.7 and an 85% response rate, we expect to have a minimum of 140 lung cancer cases and 560 controls, yielding a power of 80% to detect a trend in odds ratios of 2.0 for high exposure, 1.4 for low/moderate exposure, and 1.0 for no exposure, after adjustment for smoking ($\alpha = 5\%$). (The power will be better than 95% for detection of a trend in odds ratio from 1.0 to 1.6 to 2.5.)

Information from comprehensive industrial hygiene surveys at each working mine and data from past surveys, together with information on diesel usage and other surrogate measures, will be used to construct estimates of personal exposure for input into the cohort and case-control studies. The measurements will include elemental carbon (currently considered the most specific measure of general diesel exhaust exposure), submicrometer combustible dust, submicrometer particulate, the organic fraction of the exhaust, NO, NO_2, CO, CO_2, nitro-polycyclic aromatic hydrocarbons (nitro-PAHs) and respirable and total particulate. Information on the operating and organizational structure of each mine, together with the sampling results, will be used to define uniform exposure categories (either job-based or zone-based). Using a program developed by NCI specifically for retrospective exposure estimation, this information will be combined with data on significant change periods to develop a matrix of exposure levels by exposure category (zone or job). Then, by employing an exposure category/job dictionary and the job history for each person, individual exposure estimates will be developed. More detailed exposure information will be collected for each subject in the nested case-control study in order to refine the exposure estimates.

The purpose of the biomarker study is to examine whether workers exposed to diesel exhaust have detectable levels of nitro-PAH metabolites in their urine and nitro-PAH DNA adducts in a spectrum of tissues, and to relate these to airborne exposures. This study will provide information on biologic indicators of exposure and give insight into the early biologic effects of diesel exhaust exposure. It will thus help in the understanding of the biologic relevance of various components of diesel exhaust. A total of 160 workers will be enrolled into four study groups formed by the combination of diesel exhaust exposure (high, none) and tobacco use (yes, no): 50 high, yes; 50 high, no; 30 none, yes; and 30 none, no. Blood, sputum, and urine samples will be collected. It is planned to measure urinary metabolites of nitropyrenes (e.g., 1-acetylamino-6(8)-hydroxypyrene), and also to assess nitro-PAH DNA adducts in exfoliated bronchial epithelial cells, in exfoliated urothelial cells, and in white blood cells. This information will be correlated with personal air monitoring levels of constituents of diesel exhaust.

2. BACKGROUND

Diesel exhaust is an air pollutant that has been classified as a potential carcinogen in humans by the National Institute for Occupational Safety and Health (NIOSH),[1] and as a probable carcinogen in humans by the International Agency for Research on Cancer (IARC),[2] because of the excesses of lung and bladder cancer found among workers with long-term exposure and the development of cancers seen in some experimental studies. The carcinogenicity of diesel exhaust is not only a concern for the 1 million or more workers who are occupationally exposed to diesel exhaust, but also for the general population. Background concentrations of diesel exhaust particles on major highways in urban areas have been shown to be about twice those in residential areas.[3] Thus, long-term commuting by automobile may expose an individual to appreciable levels of diesel exhaust exposure.

2.A Constituents of diesel exhaust

Diesel exhaust consists of particulate matter and various gases and vapors. Typically, much of the particulate is composed of elemental carbon, formed through incomplete combustion of the fuel. The particulate is fine, with 95% being less than 1 μm in size.[4-6] The particles have a high surface area, permitting the adsorption of the thousands of different substances produced during combustion, including polycyclic aromatic hydrocarbons. Many of these substances are mutagenic or carcinogenic.[7] Thus, owing to the respirable nature of the particles and the toxicity of the compounds attached to them, diesel exhaust appears to have a high potential for causing health effects such as lung cancer. In contrast to the particulate, the gases and vapors in the diesel exhaust (e.g., carbon monoxide, nitrogen oxides, sulfur dioxide, and irritants such as ammonia and acroleins) are not thought to be strong mutagens or carcinogens at the levels at which they occur.[8]

2.B Experimental evidence of carcinogenicity of diesel exhaust

In 1985, McClellan and co-workers[9] summed up the biologic activity of diesel exhaust particulate extracts as follows:

> *In 1977, the U.S. Environmental Protection Agency issued a precautionary notice stating that organic solvent extracts of diesel soot were mutagenic in bacteria. Since then numerous reports ... have explored the mutagenicity of diesel soot extracts and their individual constituents.*
>
> *The potency of extracts of diesel exhaust particles in the bacterial mutagenicity has been compared with that of extracts of known human carcinogens. Diesel exhaust particle extracts have about the same potency as coke oven emissions and typically are more potent than cigarette smoke and roofing tar. Certain families of compounds in the diesel soot extracts, such as nitropyrenes, are particularly potent bacterial mutagens and principal contributors to the mutagenicity of the whole extract. Diesel soot extracts have also been found to cause mutations in cultured mammalian cells. These positive results in the mutagenicity assays warn of potential carcinogenicity. Skin tumor initiation assays with diesel exhaust particle extracts indicate a potency for skin tumor induction somewhat lower than that of coke oven emissions.*

Despite these clear indications of biologic effects associated with diesel exhaust, findings from animal experiments have been less striking. Experiments involving airborne exposure to diesel exhaust have

been conducted in rats, mice, and hamsters. In five studies of Syrian golden hamsters, involving four types of diesel engines running at different operating modes, and leading to a range of diesel soot concentrations from 0 to 6.6 mg/m^3, the results were almost uniformly negative for tumor induction.[10-13] Four studies have been reported on mice, consisting of 11 different experiments.[14-17] These used four different diesel units running at idle, constant speed, and short cycle, and leading to exposures from 0 to 12 mg/m^3 of diesel soot. In five of the experiments, more lung and other tumors were found in the exposed animal group compared to controls, while in the remaining six the controls had more or equal numbers of tumors than the exposed group. Only in rats is there reasonably consistent evidence of an effect of diesel exhaust. There were 12 such studies published in 18 reports,[12,13,15-30] involving nine types of diesel engines running in various operating modes, generating diesel soot airborne concentrations ranging from 0 to 8.3 mg/m^3. Most of the studies showed elevated numbers of tumors in the exposed group compared to controls as long as the exposure was 1 mg/m^3 or greater. In three of the five studies having multiple exposure levels there was evidence of an exposure-response trend across four or five exposure groups,[22-25] although it was totally consistent in only one of these.[22,23] Recently, researchers have turned to investigating the role of particle overload in causing lung cancer.[31,32] Although this effect has been demonstrated in rats, it has been found that rats respond similarly to a wide range of dusts, including some expected to be benign. Hence, the relevance of these findings to humans is questionable.

Reviewing the findings from animal experiments, Mauderly[8] concluded that *"diesel exhaust is a pulmonary carcinogen when inhaled chronically at high concentrations by rats, is of questionable carcinogenicity in mice, and is not carcinogenic in Syrian hamsters."* In view of the indicative, though inconclusive, findings in animals, there is a clear need for more information on the effect of diesel exhaust exposure in humans.

2.C Epidemiologic evidence for health effects

2.C.1 Cohort mortality studies

Findings from 18 mortality studies pertaining to the question of lung cancer and diesel exhaust are summarized in Table 2.1.[33-50] In 14 of the 18 studies, one or more SMR or RR was greater than 1.00, although a statistical significant excess risk (at the 5% level) was achieved only in six of the 16 in which tests were undertaken. For bus workers (including various groups of drivers, conductors and maintenance workers) there was no clear indication of excess risk, the overall risk ratios ranging from 0.66 to 1.42.[33-37,41] Results from the seven studies that investigated truck drivers revealed a more consistent pattern of mortality, showing risk ratios between 1.15 and 1.65.[38-41,48-50] The findings for railroad workers were positive in three out of four studies (risk ratios varying from 0.72 to 1.59).[42-44,48] Among the other occupations studied, an excess risk was evident in dock workers,[46] but was not obvious for heavy equipment operators.[45] In the only study of underground non-metal miners,[47] there was no clear evidence of excess risk of lung cancer. However, the study was small, and the follow-up period was probably inadequate given the typical latent period for lung cancer in humans.

In general, the studies had five major weaknesses. First, only one was able to adjust for smoking. Second, most defined exposure based on job information, and none had incorporated quantitative estimates of diesel exhaust exposures directly into the mortality analysis. Third, exposure to diesel exhaust appeared to be low generally. Fourth, the latency in many studies may have been insufficient to detect excess lung cancer

Table 2.1 Summary of published information from cohort studies

Authors (Date)	Work Force	Number	Person - years	Follow - up time	Exposure basis	Findings for lung cancer	Comments
Raffle[33] (1957)	Bus transport employees	NK	61,585	1950-54	Job	MR=1.2 and 0.7 for engineering staff and bus drivers, respectively, aged 45-64	No statistical significance tests. Short follow-up period.
Waller[34] (1981)	Bus transport employees	NK	420,669	1950-74	Job	MR=0.75, 0.75, 0.90, and 0.66 for bus drivers, conductors, garage engineers, and central works engineers. Underground workers had similar MRs	Short follow-up period.
Rushton et al.[35] (1983)	Bus maintenance workers	8,684	50,008	1967-75	Job	SMR=1.01	Short follow-up period.
Edling et al.[36] (1987)	Bus garage employees	694	20,304	1951-83	Job	SMR = 0.70. No different from clerks, and similar across subgroups of high exposure and latency	Small study.
Gustavsson et al.[37] (1990)	Bus garage workers	708	21,375.5	1952-86	Semi-quantitiative based on tenure and job	SMR=1.22 overall, and 1.27 for heaviest exposed group.	Small study.
Leupker & Smith[38] (1978)	Truck drivers	183,791	NA	1976	Job	SMR=1.21	Based on annualized data from three months of 1976.
Ahlberg et al.[39] (1981)	Truck drivers	35,883	NA	1961-73	Job	RR=1.33* for 'ordinary' truck drivers compared to nonexposed group. RR=1.62* compared to Stockholm males.	Smoking not thought to be responsible for excess.
Hansen[40] (1993)	Truck drivers	14,225	138,302	1970-80	Job	SMR=1.60*. Indication of increase with age.	Compared to a nonexposed group of 38,301 workers with similar lifestyle.
Balarajan & McDowall[41] (1988)	Professional drivers	3392	NA	1950-84	Job	SMR=0.86, 1.42, and 1.59 for taxi, bus, and truck drivers,	Use of national rates for adjustment might overestimate SMRs.
Kaplan[42] (1959)	Railroad workers	32,000 approx.	235,000 approx.	1953-58	Job	SMR=0.88 and 0.72 for engine and train service, and shop, respectively	
Howe et al.[43] (1983)	Railroad workers	43,826	290,185	1965-77	Jobs classified into exposure groups.	RR=1.20 and 1.35 for possible and probable exposure to diesel relative to no exposure	Possible confounding with asbestos?
Garshick et al.[44] (1988)	Railroad workers	55,407	NA	1959-80	Dichotomous based on job in 1959, and on years of exposure since 1959.	RR=1.45*, 1.33*, and 1.12 for ages 40 - 54. Indication of trend with years of diesel exposure	Missing death certificates in 12%.
Wong et al.[45] (1985)	Heavy equipment operators	34,156	372,525.6	1964-78	All workers. Duration of exposure and latency considered.	SMR=0.99 overall. Indication of trend with latency, and elevation among higher exposed and retirees, though no trend with exposure category.	

Table 2.1 Summary of published information from cohort studies - continued

Authors (Date)	Work Force	Number	Person - years	Follow - up time	Exposure basis	Findings for lung cancer	Comments
Gustafsson et al.[46] (1986)	Dock workers	6,071	97,076	1961-81	All workers	SMR=1.32*. Morbidity rate higher	
Waxweiler et al.[47] (1973)	Potash miners	3,886	53,587	1941-67	All workers	SMR=1.08 overall. No trend with tenure group	Short follow-up period.
Boffetta et al.[48] (1988)	General population	476,648	939,817	1982-84	Stated exposure to diesel exhaust	RR=1.18 for diesel exposure adjusted for smoking and other exposures. RR=1.59, 1.24, 2.60*, and 2.67*for railroad worker, truck driver, heavy equipment op., and miner, respectively.	Volunteers (possible bias?). Adjusted for smoking.
Lindsay et al.[49] (1993)	General labor force	415,309	5,468,265	1965-79	Job	SMR=1.15*for truck drivers	
Menck & Henderson[50] (1976)	General labor force	Estimated	Estimated	1968-73	Job	SMR=1.65 for truckers	Populations at risk estimated from census data.

* indicates statistical significance at 5% level or greater RR=Relative risk. SMR=Standardized mortality ratio. MR=Mortality ratio.

mortality. Finally, confounding from other exposures, such as asbestos, was an unresolved difficulty in a number of studies. These weaknesses make it difficult to draw reliable conclusions from these findings.

2.C.2 Case-control studies

Findings from 17 case-control studies are given in Table 2.2.[37,51-66] In contrast to the findings from cohort studies, elevations in risk associated with diesel exposure (odds ratio (OR)>1.0 or relative risk (RR)>1.0) were evident in every study, and statistically significant findings (at the 5% level) occurred in nine of the seventeen. Although most risk estimates varied between 1.1 and 1.9, higher estimates were found among sub-groups with longer or greater diesel exhaust exposure. Among these were RR = 4.5 for older drivers,[67] RR= 2.6 for the highest exposure group among bus garage workers,[37] and OR = 2.4 for those with 31+ years of exposure.[63] Smoking was taken into account in all but three studies, but confounding from other exposures was considered only in two.

As in the cohort studies, exposure information on diesel exhaust was generally weak, often being based on job title or industry. However, current measurements of diesel exhaust or surrogate estimates were employed to classify levels of exposure in four studies.[37,58,64,66] Among these, railroad workers[58] and truck drivers[64] had modest increases in risk (RR = 1.41 for 20+ diesel-years of exposure in younger railroad workers, and OR = 1.89 for 35+ years as a driver of diesel trucks).[a]

2.D Summary of epidemiologic findings

Overall, currently available epidemiologic information suggests a moderate increase in risk of lung cancer at the levels of exposure experienced among the studied workers. The existing studies, however, have many weaknesses. In particular, most relied on rather crude indicators of diesel exhaust exposure, and no study employed historical quantitative measurements of diesel exhaust. In addition, short follow-up period, low exposure levels, and small numbers of observations may have led to low power for many studies, while lack of adequate control for confounding has been a problem in some.

is because of the drawbacks in existing studies that NCI and NIOSH propose to conduct a cohort and nested case-control study of lung cancer among non-metal miners.[b]

3. FEASIBILITY STUDY

In 1992, NCI and NIOSH initiated a study to evaluate the feasibility of a nested case-control study of lung cancer among diesel-exhaust exposed miners. The purpose of the feasibility study was to determine: 1) the number of non-metal miners exposed to diesel exhaust in underground mines between 1960 and 1979; 2) the completeness of the work history data available since diesels were introduced into the mines; 3) whether work history data contain possible exposure surrogates (such as job title, department, equipment

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[a] The findings from the other two studies appear to be somewhat stronger, i.e., OR = 2.4 for bus workers,{{Gustavsson1990}} and OR = 6.8 for dock workers.{{Emmelin1993}} However, the former study did not control for smoking, while the latter study is based on only 50 cases.

[b] The term 'non-metal' is conventionally used in connection with mineral mines (salt, potash, trona, etc) as opposed to 'metal' mines, in which the ore is refined to produce metals such as copper, gold, zinc, etc. Silica and radon exposures (among other possible or potential carcinogens) are typically much greater in metal mines than they are in non-metal mines.

Table 2.2 Summary of published information from case-control studies

Authors (Date)	Cases	Referents	Number cases	Number referents	Exposure basis	Matching	Findings for lung cancer**	Comment
DeCoufle et al.[51] (1977)	Male patients with lung CA	Non-neoplastic disease patients	191	NA	Job	Unmatched	RR=1.75, 1.75, 1.50, and 1.35 among bus, taxi, and truck drivers and locomotive engineers, respectively, aged 60 or greater. Smaller RRs in younger workers, some <1	Selected occupation compared to clerical workers. No control for confounders
Williams et al.[52] (1977)	Lung CA patients	Other cancer patients	432	7,086	Job and industry	Unmatched	OR=1.52* for trucking industry	Control for alcohol and SES.
Milne et al.[53] (1983)	Lung CA deaths	Deaths from other cancers	925	6,565	Job and industry	Unmatched.	OR=3.5* and 1.6 for bus drivers and truck drivers, respectively. ORs elevated for other diesel-related jobs (NS)	No adjustment for smoking
Coggon et al.[54] (1984)	Lung CA deaths	Deaths from other causes	598	1,180	Job	Sex, death year, region, and birth year (approx.)	RR=1.3* for all jobs with diesel exposure. RR=1.1 for high exposure	No allowance for smoking. Young workers. Reliance on most recent job
Hall & Wynder[55] (1984)	Hospitalized males with lung CA	Hospitalized males with no tobacco related diseases	502	502	Job	Age, race, hospital, and hospital room status	RR=1.4 for total diesel exposed and for truck drivers. Larger RRs (up to 2.1) for other occupations but low numbers	Small numbers. Confounding with other exposures? Not adj for smoking
Buiatti et al.[56] (1985)	lung CA cases.	Non-LC patients	376	892	Job	Sex, age, admission date, smoking status.	OR=1.1 and 1.8* for transportation workers, and taxi drivers respectively	Frequency matching used
Damber & Larsson[57] (1985)	Male patients with lung CA	One living and one deceased without LC	604	1,071	Job, with tenure	Sex, death year, age, municipality	RR=1.9 and 4.5* in non-smoking drivers and truck drivers aged<70 and >=70 respectively	Ex-smokers for 10 years included with non-smokers
Garshick et al.[58] (1987)	Deaths with primary lung CA among railroad workers	Deaths from other than cancer, suicide, or accidents	1,256	2,385	Job based on current measured exposure levels, with tenure	Date of birth and death	RR=1.41* for 20+diesel-years in younger workers (<=64), RR= 0.91 for older workers	Adjustment made for asbestos exposure. Nested within cohort study by Garshick et al. (1988)
Lerchen et al.[59] (1987)	Persons with lung CA	Medicare recipients	506	771	Job and industry	Sex, age, ethnicity	OR=0.6 for those with exposure to diesel fumes. OR=1.9* for underground miners.	Not matched on date of birth or death
Benhamou et al.[60] (1988)	Histologically confirmed lung CA	Non-tobacco related diseases	1,625	3,091	Job	Sex, age at diagnosis, hospital and interviewer	RR=1.42* for motor vehicle operators	
Siemiatycki et al.[61] (1988)	Lung CA cancer patients by type of lung CA	Other cancer patients	159 - 359	1,523	Exposure to diesel exhaust.	Unmatched	Squamous cell LC OR=1.2 for diesel exhaust exposure, overall, and 2.8 for mining and quarrying. ORs lower for other LC types.	Number of cases depends on LC type

Table 2.2 Summary of published information from case-control studies - continued

Authors (Date)	Cases	Referents	Number cases	Number referents	Exposure basis	Matching	Findings for lung cancer**	Comment
Hayes et al.[62] (1989)	Lung CA deaths	Various - lung disease excluded	2,291	2,570	Job, with tenure	Sex, age, and various	OR=1.5* approx. for 10+ years tenure. Elevation evident in most occupational groups studied	Composite of three studies. Exposure not specific to diesels, but includes gasoline
Boffetta et al.[63] (1990)	Hospitalized males with lung CA	Hospitalized males with no tobacco related disease	2,584	5,099	Job. A subset had tenure	Sex, age, hospital, year of interview	OR=1.2 for self-reported exposure, which was mostly due to OR=2.4 in longest exposed group	
Gustavsson et al.[37] (1990)	Deaths from lung CA among bus garage workers	Non-cases within cohort mortality study	20	120	Semi-quantitiative based on tenure and job	Born within two years of case	RR= 1.27, 1.56, 2.63 for increasing diesel exhaust index category relative to lowest level.	Nested case-control study within cohort mortality investigation. Weighted RR analysis appears to be in error. No control for smoking.
Steenland et al.[64] (1990)	Deaths from lung CA among Teamsters	Deaths excluding LC, bladder cancer, and motor vehicle accidents	996	1,085	Job and tenure, later supplemented by IH data.	Unmatched	OR=1.27, 1.31, 1.69, 0.92, and 1.44 for long and short haul drivers, truck mechanic, dock worker, and other diesel exposed. OR=1.89* for diesel truck drivers with 35+ years of employment.	Short follow-up period.
Morabia et al.[65] (1992)	Male lung CA patients	Patients without LC	1,793	3,228	Job, with coal and asbestos exposure durations.	Race, age, hospital, and smoking history	OR= 2.3 and 2.4 for mine and transportation operatives	Not diesel specific. Confounding from other exposures?
Emmelin et al.[66] (1993)	Deaths from primary lung CA among dock workers	Non-cases surviving to case's date of diagnosis	53	154	Job, with tenure and historic fuel usage	Date of birth, port, and survival to within 2 years of diagnosis of LC	Apparent RR trend with exposure level for three different exp. estimates. RR=2.9 for longest exposure level.	Case-control study nested within cohort study by Gustafsson et al. (1986)

* indicates statistical significance at 5% level or greater
** RR=relative risk, OR=odds ratio

assignment, work area) that could be used to develop individual exposure estimates; and 4) availability of historical industrial hygiene data on diesel exposure and the feasibility of using these data, as well as It current exposure data, to estimate past exposure. The feasibility effort was conducted in two phases from 1992 to 1994. Non-metal mines were selected that had documented low levels (<0.1 WL) of radon. In Phase I, a telephone survey of the 41 U.S. underground non-metal mining operations that actively employed 50 or more employees was made to identify mines that had used diesel equipment for at least 10 years prior to 1980. Based on the telephone survey, 24 mines were chosen for site visits (Appendix A). Information from the site visits was used to rank the 24 mines for suitability for the main study (Appendix B). Phase II of the feasibility study was a comprehensive industrial hygiene survey of current and past exposure to diesel exhaust at one mine. This demonstrated that it was possible to link job history information collected from personnel records with environmental exposures measured both during 1976-1978 and currently.

4. STUDY OBJECTIVES AND OUTLINE

4.A Justification

Few mortality studies using quantitative measures of diesel exhaust directly to assess exposure-response exist. Those that do have defects and are incomplete. For this reason, NIOSH and NCI propose to undertake a comprehensive study to investigate lung cancer mortality and diesel exhaust exposure. The findings from the feasibility study indicate that a cohort and a nested case-control study of lung cancer among non-metal miners who have been exposed to diesel exhaust is feasible. Non-metal miners are an optimal study group to evaluate the relation between diesel exhaust exposure and lung cancer risk for several reasons. First, the feasibility study indicated that diesel exposure among the underground mining population is 5 to 40 times greater than that observed in other diesel-exposed populations. The high exposure levels will facilitate detection of exposure-response if such truly exists. Two surrogates of diesel exhaust exposure are nitrogen dioxide (NO_2) and elemental carbon. Woskie et al.[68] measured NO_2 levels at railroad yards and found arithmetic mean exposures of 111 ppb (SD = 104) for the highest exposure group (mechanic shop workers). During our feasibility study, we measured personal NO_2 exposures at one potash mine and found an arithmetic mean of 527 ppb (SD = 211) for the underground production workers.[c] Those heavily exposed workers (the belt crew) had average NO_2 exposures of 780 ppb (SD = 313). Submicrometer elemental carbon levels averaged 5.1 micrograms per cubic meter ($\mu g/m^3$) (SD = 3.4) for road (long distance) drivers in the trucking industry.[69] By comparison, underground production workers during our feasibility study were exposed to an average concentration of 237 $\mu g/m^3$ of elemental carbon (SD = 171), while underground foreman and maintenance workers had mean exposures of 160 and 50 $\mu g/m^3$ respectively. Second, this is the first cohort with adequate information to quantify historical exposures to diesel exhaust. The historical exposure assessment is particularly strengthened by the availability of industrial hygiene (IH) data from surveys carried out at non-metal mines in 1976 (Section 8.C.6.a). Third, the follow-up period for the cohort ranges up to 45 years, which should be sufficient to detect an elevation in lung cancer mortality. Fourth, information on cigarette smoking and other potential confounders will be obtained and controlled for in the analysis.

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[c] All underground workers apart from foremen and maintenance workers.

4.B Primary objectives

The principal objectives of the study are as follows:

i) To evaluate mortality, particularly from lung cancer, with regard to diesel exhaust exposure among non-metal miners, standardizing for age, smoking, and other potential confounders.

ii) To determine whether lung cancer mortality increases in relation to level of exposure to diesel exhaust after controlling for age, smoking, and other potential confounders.

iii) To evaluate the association between measured levels of diesel exhaust components in the air and: a) nitro-PAH derived metabolites in the urine, and b) DNA adducts in exfoliated epithelial bronchial and urothelial cells and peripheral white blood cells, using samples from miners who are currently occupationally exposed to diesel exhaust and from those who are not exposed.

4.C Study overview

The study will consist of a cohort mortality study, a nested case-control study based on lung cancer cases identified in the cohort study, and a biomarker study. Large mines (> 50 employees) known to have low levels of potential confounders (e.g., silica and radon) and moderate to high levels of diesel exhaust underground were selected as potential mines for study. Previous investigation has shown these mines to have suitable and comprehensive personnel records. Ten of these mines are expected to provide records for over 8,000 miners for input to a cohort mortality study (184,000 or more person-years).[d] An exposure assessment will be undertaken at each operating mine, and quantitative as well as cruder surrogate measures of worker exposures developed.

4.D Study power

The cohort study was designed to be large enough to provide sufficient cases for a case-control study of adequate power. For this reason, the following statement and discussion of power concentrates on the case-control study. However, it should be noted that the cohort study has greater than 90% power to detect a trend in RR from 1 for nonexposed to 1.4 for low/moderate exposure to 2.0 for high exposure, based on a 5% alpha level, and assuming 50% nonexposed, 25% low/moderate exposed, and 25% high exposed.[e] The power curve for the case-control study is shown in Figure 4.1. This shows that at a 4:1 matching ratio, an alpha level of 5%, an OR of 1.4 and 2.0 for the low/moderate and high exposure groups, respectively, and exposure distribution as noted above, the case-control study would have close to 80% power. Use of matching ratios less than 4:1 would provide unacceptably low power (especially for 2:1 or less). If the trend is 1 to 1.6 to 2.5 (an overall doubling in risk) with increasing exposure level, the power increases to over 95%. Finally, the power to detect an overall OR of 1.5 (i.e., OR = 1.3 and 1.7 for low/moderate and high exposure) is better than 50%.

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[d] Record collection will be organized such that mines of greatest utility to the study (i.e., with the highest exposures and best IH and personnel records) will be visited first. Record collection will be terminated as soon as we determine that the study will provide sufficient cases for the case-control study (see section 4.D). It is expected that only ten mines will have to be visited, and even fewer may be needed.

[e] The distribution of workers across the exposure groups was evaluated using the feasibility study information. Table A.1 in Appendix A shows part of this information (the percentage of workers underground, i.e., exposed to diesel exhaust, at each mine). This amounted to about 40% of the total, with 10% more coming from diesel exposed workers on the surface.

4.E Study duration

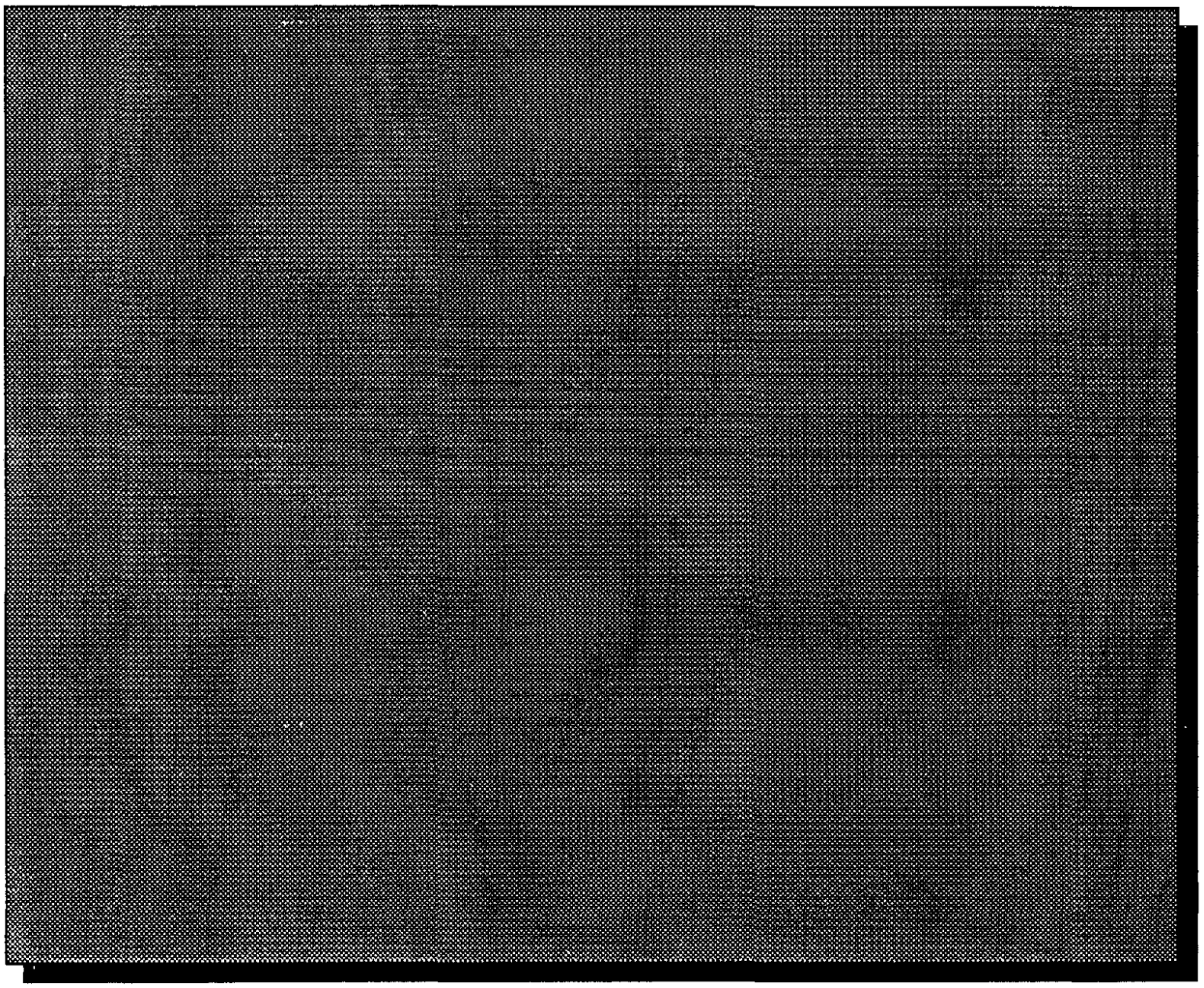

Figure 4.1 Power by odds ratio, with stratification by smoking, for various matching ratios. L=low/moderate exposure; H=high exposure.

A time-line showing the schedule of major activities in the study is given in Figure 4.2. We estimate that the cohort mortality study will require two years for data collection and processing, followed by one year for completion of mortality follow-up and death certificate acquisition activities. (These estimates are based on the extensive experience gained with data collection and processing for the feasibility study data and for other mortality studies.) When the mortality follow-up is complete, a Phase I analysis will be undertaken using indirect surrogates of exposure, such as tenure and occupation. (It may be possible to employ IH data existing at the time in order to inform the choice and format of these exposure surrogates.) Results from this analysis are expected to be disseminated at the end of year 5 of the study. Work on identifying cases and controls will progress concurrently with the mortality follow-up and death certificate acquisition. When the case-control data are available, which is expected to be at the start of

the fourth year of the study, a Phase I analysis will be undertaken involving semi-quantitative exposure-response analyses based on the IH data available at that time.

The IH surveys will be conducted during the first two years. This will be followed by work on developing individual exposure estimates. The final cohort and case-control reports from Phase II of the analysis, each incorporating detailed quantitative exposure-response analyses, should be available in six years after start of data collection. The biomarker findings are expected to be ready for dissemination about four years fter protocol approval. A more detailed schedule of activities is given in Section 13.

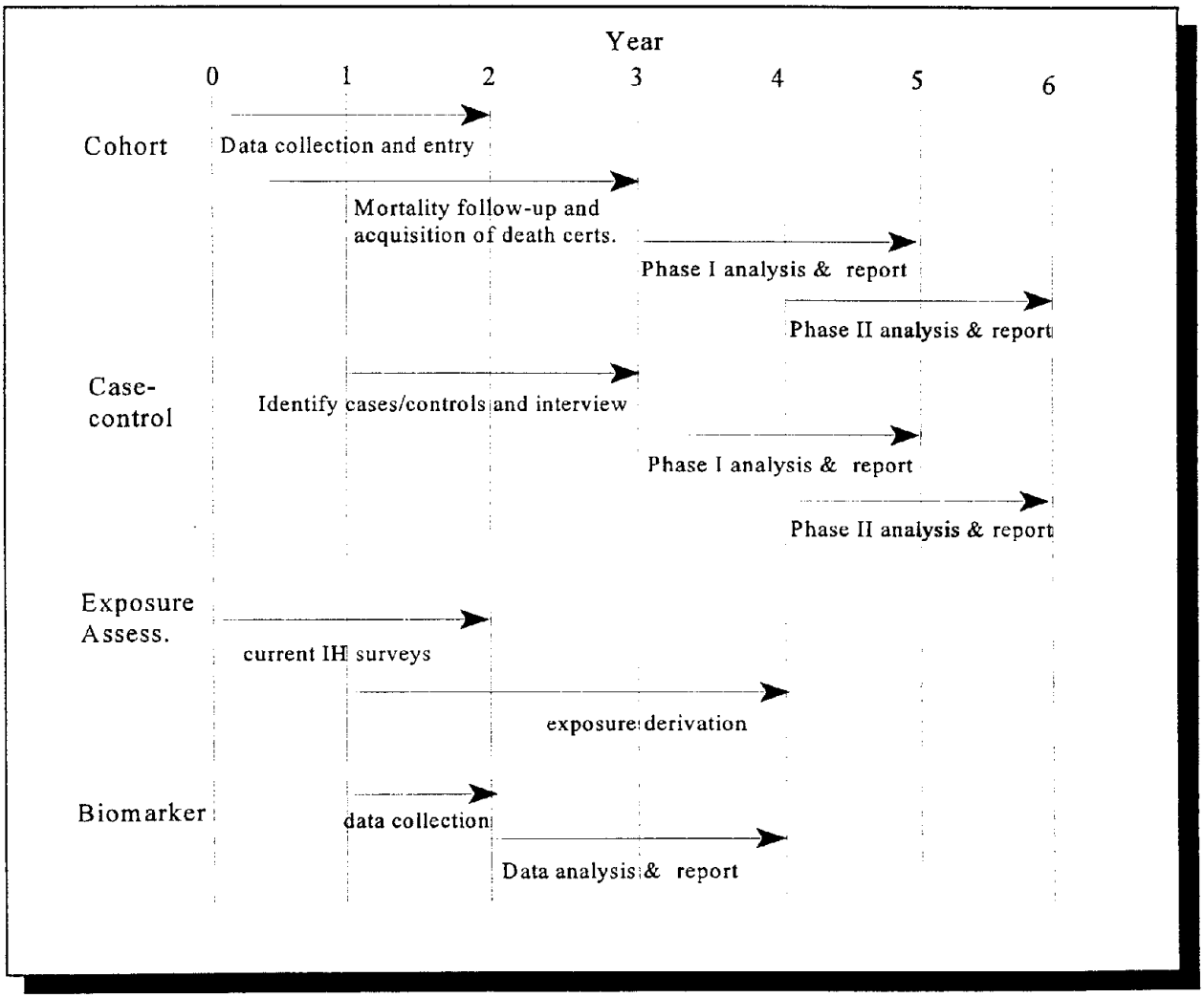

Figure 4.2 Time line showing major activities

5. COHORT STUDY

5.A Introduction

The main purpose of the cohort study is to identify causes of death (especially lung cancer) that are elevated in the cohort with regard to extent of diesel exhaust exposure. Both external and internal comparisons will be made. Internal contrasts of exposed versus nonexposed miners and trend analyses will be conducted to identify causes of death in relation to degree of diesel exhaust exposure.

The study cohort will be comprised of underground, and surface workers (excluding administrative workers) who have been employed in the candidate non-metal mines for at least one year during the period between the date of dieselization of each mine and December 31, 1996. A selection criterion of one year of employment during diesel use in the mines will be applied to ensure a reasonable minimum period of exposure. Most surface workers are essentially not occupationally exposed to diesel exhaust, thus the cohort study will include a wide range of exposure to diesel exhaust. (We estimate about 50% unexposed, 25% low/moderate exposed, and 25% high exposed expected, based on underground workers comprising about 40% of the mine work force.) The study cohort will be followed for vital status through December 31, 1996. Since the earliest date of dieselization of any of the proposed study mines was 1950, the follow-up period will range up to 45 years.

5.B Data collection and processing

5.B.1 Mine selection

Appendix B provides full information on mine selection. In brief, each of the 24 mines visited during the feasibility study was examined in terms of its inclusion in the 1976 study, current operating status, size, extent of diesel exposure, and quality of records. Account was also taken of whether any company had more than one mine among the 24. Each of these factors was tabulated and categorized. An overall mine ranking was developed based on these factors. Mines were brought into the study according to their priority ranking. On this basis, it is expected that the top 10 mines will constitute the full set of mines necessary for adequate study (about 8,200 miners and 184,000 person-years, leading to 160 lung cancer cases for an assumed RR of 1.7). However, we will evaluate the number of lung cancer cases arising and expected as follow-up progresses, and if it appears that sufficient cases will be gained, we will curtail the mine visits without going to all 10 mines. In this way, the study will be accomplished as expeditiously and efficiently as possible. If unexpected events prove that more mines might be needed, additional mines will be included until sufficient lung cancer cases are obtained for the case-control study. Appendix C shows that silica and radon levels were low in the 24 mines.

5.B.2 Data abstraction

The data from each mine will be abstracted in two phases in order to accelerate the study as much as possible. This two phase approach has been chosen to allow for vital status follow-up procedures to progress without being held back by the more lengthy task of the work history abstraction. First, information necessary for identifying the study cohort and for establishing vital status will be abstracted from microfilm once the visit to each facility is completed. To establish the criterion of one or more years of tenure, the beginning and ending dates of employment at the mines will be abstracted for each individual. Follow-up procedures will then be undertaken in batches. In the second phase, complete job

histories, previous employment histories, any available smoking information, next of kin, and any other relevant information will be abstracted. The intent is to account chronologically for each subject's total working life prior to termination of employment at the mine.

5.B.3 Coding of current and previous employment histories

Current and previous employment histories will be entered into the mortality database system (MDS). Job information will be entered directly as found in the records, as text, and will not be coded initially. Later, during the computation of worker exposures, the job titles will be scrutinized, and equivalent titles merged into a standardized system for linking with the exposure information.

5.B.4 Data entry and management

Data will be entered into the MDS, which was designed and developed at NIOSH during the feasibility study. The system is accessed from desk-top computers via the Division of Respiratory Disease Studies (DRDS) Local Area Network (LAN). It provides for independent entry by multiple abstractors, and permits edit checking and comparison and verification of records. Full back-up facilities are provided, and data can be exported for submission to various organizations for follow-up purposes.

5.B.5 Determination of cohort eligibility

Non-administrative workers who meet the one year work duration of employment criterion will be selected for follow-up. Records for workers who do not meet the one year work duration criterion at any one mine will be collated across mines to determine if they had worked at other mines. Those with work at multiple mines, whose total tenure was found to meet the 1 year work criterion will be added to the cohort. Where possible, quarterly earnings reports from the Social Security Administration (SSA) will be obtained to examine the completeness of personnel records abstracted from the companies' files.

5.B.6 Follow-up procedures

The study cohort will be followed through the end of 1996 and vital status will be assessed via the sources described below.

i) The cohort will be checked against the SSA mortality files. The MDS permits manual checking of partial matches and for indication of death to be added to the main cohort database. There are two methods used in matching the cohort data with the SSA death information tapes: a) social security numbers, and b) the first five characters of the last name together with the date of birth. In addition, NIOSH has purchased CD-ROMS of a nation-wide death index based on the SSA death-tape data from CSRA, Inc. These will be updated to include deaths up to the end of 1996 when they become available. These CD's will provide an additional means to check on the occurrence of deaths as the as the software allows for Soundex matches on names, but does not allow for large batch runs, and thus cannot at this time supplant the SSA death tape procedures.

ii) The National Death Index (NDI) established by the National Center for Health Statistics is a source of death information in the U.S. from 1979 to the present. The NDI is especially useful because it supplies the death certificate numbers, which makes the ordering of death certificates from the states easier. In addition, the NDI now has a procedure by which cause of death

information can be obtained directly, obviating the often lengthy wait for death certificates from the states. The matching algorithm used by NDI includes both exact and phonetic matching on names and is able to report possible as well as definite matches. The NIOSH MDS allows for incorporation of the NDI information into the cohort database in a manner similar to that for the SSA data matching.

iii) The study cohort members still considered alive after searches using the SSA death tape, CD-ROM database and NDI will then be checked for vital status against a number of other sources, including: a) the Internal Revenue Service (IRS), which supplies last known address (current up to the last 5 years); b) the U.S. Postal Service, which supplies the current address as well as information on vital status, if known by the local postal personnel; c) the Health Care Finance Administration; d) the individual State Motor Vehicle Registration Offices; and, e) CSRA Inc and Credit Bureaus. Labor Unions will also be contacted to determine whether their records would assist in tracing hard-to-find cases.

iv) The last fraction of the cohort needing confirmation as alive after all the above procedures have been carried out will be contacted for information. This will be done via a vital status letter (current OMB No. 0920-0035), and possibly by use of contractor services.

Once all the vital status information has been obtained, the cohort data base will be updated as to the vital status and address information, and death certificates for the remaining deceased cases will be ordered from the states.

5.B.7 Coding of causes of death and entry of death certificate information

A certified nosologist will be contracted to code the death certificates for causes of death, both underlying and contributing, using the revision of the International Classification of Disease codes applicable to the date of death. Information from the cause of death coding and the death certificates will be entered into the cohort database. Data that will be entered include: date of death, state of death, county of death, death certificate number, autopsy performed, underlying cause of death, other causes of death - up to six allowed, accident place code, date of birth, gender, race, and name and relationship of next-of-kin.

5.C Data analysis

Analysis of the cohort study will be undertaken in two phases. Phase I will employ indirect surrogates of diesel exposure in order to explore exposure-response. Finally, when individual worker exposure assessments have been developed, a full quantitative exposure-response analysis will be possible in Phase II.

5.C.1 Indices of exposure to diesel exhaust

Indirect exposure measures for Phase I of the study include work and tenure in jobs known *a priori* as having high, moderate, and low exposures (e.g., face, other underground, and surface work). It may also be possible to include preliminary data from the IH surveys and elsewhere in order to help inform and define the exposure categories.

Section 8 describes the procedural steps for the retrospective assessment of exposure to diesel exhaust. This exposure information will be applied to the Phase II analysis of mortality in the cohort study. Evaluation of exposure-response will be made using various exposure metrics, such as cumulative exposure, duration of exposure, average exposure and maximum exposure (see Stayner et al.[70]) as deemed appropriate. In addition, lagged estimates of exposure will be used to eliminate the effect of later exposures in examining the exposure-response relationship. Time-dependent aspects of exposure estimates will be accounted for where appropriate in the statistical analyses to be carried out.

5.C.2 Control for confounding

Although the mines selected for study have been documented as having low levels of exposure to radon, silica, and arsenic, we will sample for these substances and also for asbestos during the IH surveys to assure that levels are below that which might be expected to cause confounding. If unforeseen elevations occur, and it appears that confounding could be a problem, control for these variables will be included in the analysis. Although not a confounder, employment in jobs where exposure to diesel exhaust may have occurred outside of non-metal mining, such as prior employment as a truck driver, may be important, and it will be taken into account.

Since smoking is a risk factor for many diseases, it could lead to confounding of its effect and that of diesel exposure.[71] The Axelson technique[72,73] will be used to indirectly adjust for smoking for at least the U.S. reference population. For the mines that were in the 1976 MSHA/NIOSH study, there is smoking information available on the cross-section of workers who took part in the study. Information on smoking in the reference population will relate to the same time period as smoking information on the cohort. Relative risks for smoking/disease associations needed for the adjustment will be taken from the literature.

5.C.3 SMR analyses

The mortality experience of the cohort will be compared to the U.S. population and to county/state populations using the NIOSH Life Table Analysis System (LTAS)[74] and to the NCI/NIOSH Computerized Occupational Referent Population. Person-years at risk will begin at the end of the first year of work in the study mines. The accumulation of person-years will cease when an individual is lost to follow-up, dies, or on December 31, 1996, whichever occurs first. A usual SMR analysis of all causes of death that occur in the cohort with stratification by age, race, gender and calendar time will be conducted.

Further SMR analyses by various measures of exposure, such as duration of exposure, cumulative exposure and time since first exposure, will be undertaken. In this, the investigators are aware of the possible problems of validity of such within cohort comparisons of SMRs.[75] Since the version F of the LTAS allows for the calculation of standardized rate ratios (SRR) for up to 6 duration or cumulative exposure categories versus the lowest category, this will be done. For this analysis, the nonexposed part of the cohort will be used as the lowest exposure category. Any findings of elevated mortality ratios for outcomes other than lung cancer may suggest the need to evaluate these associations in more detail in future nested case-control studies, but will not be considered for detailed analysis in the present protocol. Causes of death will be divided into those of *a priori* interest and those of *a posteriori* interest. The former comprise: lung cancer; bladder cancer, kidney cancer, colon cancer, cancer of the rectum, multiple myeloma, lymphoid leukemia, Hodgkin's disease; cerebrovascular disease, arteriosclerosis,

pneumonia, influenza, cirrhosis of the liver, emphysema, and chronic respiratory disease. Excesses of these causes have been found in one or more studies that have looked at mortality and exposure to diesel exhaust.[2,43,45,48,76] *A posteriori* causes will be considered as hypothesis generating.[77]

5.C.4 Regression analyses

Poisson regression will be used for direct comparison of exposed and nonexposed study cohorts, and will allow for an exposure-response analysis. Variables to be investigated in the models include the various exposure indices, race, sex, age at follow-up, calendar time, previous employment in high-risk occupations for lung cancer, and previous occupational exposure to diesel exhaust. If necessary, information on radon, arsenic, silica, or asbestos will also be included in the models. Interactions of exposure variables with other independent variables, such as age and previous employment in high-risk occupations, will be investigated. The Poisson modeling will concentrate on internal analyses, but some external adjustment modeling will be undertaken using U.S. mortality rates for expected values. Cox proportional hazards regression will be used in addition to the Poisson regression to allow for the modeling of exposure and other factors, such as age at first exposure, as continuous variables. EGRET[78] will be used to carry out the Poisson regression and the Cox proportional hazards regression. The regression analyses will be carried out on underlying causes of death, and repeated for underlying and contributing causes combined. Consideration will also be given to fitting biologically-based mathematical models of carcinogenesis.

6. CASE-CONTROL STUDY

6.A Introduction

The main purpose of the nested case-control study is to evaluate the association between levels of diesel exposure and lung cancer mortality among miners, while controlling for potential confounders. Evaluation of the potential for confounding in the cohort study is either not possible or can be done with less precision than in the case-control study. Because data on exposure to diesel exhaust and potential confounders will be obtained specifically for each subject included in the nested case-control study, historical exposure to diesel exhaust will be more accurately quantified and confounding will be more completely controlled in the case-control study.

6.B Identification of lung cancer cases and selection of controls

6.B.1 Lung cancer cases

Cases from each mine will be all lung cancer deaths (ICD-O = 162) as specified on the death certificate (underlying or contributing cause) occurring among members of the cohort working at that mine between the date of dieselization of the mine and December 31, 1996. The proposed cohort is expected to yield at least 160 lung cancer deaths, based on the assumption of a doubling of risk in the high diesel exhaust exposed group (i.e., an overall OR = 1.7 for all exposed workers).

Pathology slides of tumor tissue from all histologically confirmed cases of lung cancer will be obtained for review. The objective of the slide review is to confirm the death certificate diagnosis of lung cancer as well as to determine the histologic subtype. In the absence of slides, pathology reports will be considered acceptable confirmation of diagnosis. Clinically diagnosed cases (i.e., cases with no slides or

pathology report) will be included in the analysis. We will exclude cases that are found either not likely to be carcinoma of the lung or metastatic to the lung by slide review or pathology report. Consideration will be given to undertaking histologic subtype-specific analyses if sufficient usable slides can be obtained Death certificate information will be used to ascertain whether the death was an in-hospital death or if an autopsy was performed. The identified hospital's pathology department will be contacted to request any autopsy/surgical, pathology/cytology material pertinent to the diagnosis of lung cancer. All slides of available pathologic material will be reviewed by an experienced surgical pathologist/cytopathologist who is board-certified in anatomic pathology and cytopathology. The slides will be classified as to type of lung cancer (squamous cell carcinoma, adenocarcinoma, small cell undifferentiated carcinoma, large cell undifferentiated carcinoma, mixed, other) utilizing World Health Organization criteria. .

The feasibility of analyzing the pathologic samples for evidence of potential confounders, e.g., extent of internal dose of asbestos fibers, silica, and other particulates will be explored. In addition, consideration will be given to undertaking a comparison of tumor characteristics at the molecular level (e.g., oncogene and tumor suppressor gene mutations) by identifying a series of lung cancer cases without diesel exposure, matched to exposed cases on hospital, smoking history, age, gender, and race.

6.B.2 Selection of controls

Four controls will be selected for each case by random sampling from among all members of the study base who were alive prior to the day the case died (i.e., incidence density sampling). Controls will be individually matched to the case on mine, gender, race/ethnicity (i.e., white, African-American, American Indian, Hispanic), and year of birth (within 5 years). Exposure in the controls will be truncated at the age that the case died. The necessity of selecting four controls will be evaluated and any necessary modifications made to the matching strategy following enumeratation of the cohort by mine, gender, race/ethnicity and age.

6.C Data collection and processing

6.C.1 Questionnaire

A structured questionnaire will be developed to elicit information on the following factors: date of birth, date of death, race/ethnicity, gender, history of smoking (i.e., age started smoking, number of years smoked, and usual and lifetime amount smoked), exposure to environmental tobacco smoke, dietary factors (i.e., consumption of fresh fruits and vegetables), lifetime employment history (i.e., work in mining, employment in high-risk occupations for lung cancer, asbestos exposure, silica exposure, pesticide exposure, employment in other occupations with potential for diesel exhaust exposure (bus driver, truck driver, vehicle mechanic, heavy equipment operator, and railroad worker), medical history (i.e., asbestosis, silicosis, emphysema, and other respiratory diseases). Smoking histories will be supplemented with relevant information from company medical records, smoking data collected during the 1976-78 cross-sectional morbidity survey, and interviews with co-workers.

6.C.2 Interview

The questionnaire will be administered to next-of-kin of cases and deceased controls by telephone using interviewers trained for this purpose. Information on next-of-kin will be sought first from death

certificates or employment records. We will attempt to locate and interview relatives in the following order of preference: spouse of the decedent, child, sibling, or other close relative. Direct interviews will be conducted with living controls by telephone. Informed consent will be obtained from all respondents before the interview is conducted. Based on data from previous studies, we anticipate a 75% response rate for the next-of-kin interview. We expect to obtain smoking history data on an additional 10% of subjects when the interview data are supplemented with data from additional sources (see Section 6.C.1), yielding a total response rate of 85%.

A training manual will be developed using previous case-control studies with telephone interviews as models. This manual will be used to train interviewers in structured telephone interviewing techniques. Special instruction will be given in standardized techniques to be used for probing for answers to questions answered with "don't know" or "don't remember". Every effort will be made to blind the interviewers with regard to case/control status.

6.D Data Analysis

All collected data will be edited and coded by the contractor, drawing upon experience in editing and coding of data in previous studies, and then keypunched. A computer-readable database will be established that will be suitable for statistical analysis.

Data analysis will proceed in two stages. In Phase I. a semi-quantitative analysis will be undertaken based on the IH information available at the start of year 4 of the study. Phase II will include a full examination of the data using quantitative exposure estimates derived for each individual in the study.

Data from the case-control study will be used to estimate the risk of dying from lung cancer associated with exposure to several measures of occupational exposure to diesel exhaust -- average intensity of exposure, duration of exposure, cumulative exposure, and time weighted cumulative exposure (see Section 8). The exposure estimates in the case-control study will be based on each subject's unique employment history. Conditional logistic regression analysis will be used to quantify the exposure-response relationship between lung cancer and these measures of diesel exhaust exposure after adjustment for confounding factors. The following potential confounders will be considered for inclusion in the analysis: smoking history (active and passive), history of employment as a uranium miner or in other high-risk occupations for lung cancer, asbestos exposure, silica exposure, pesticide exposure, specific medical conditions, and diet. Temporal factors related to diesel exposure, such as age at first exposure and time since last exposure, also will be examined in relation to lung cancer risk. The role of cigarette smoking as a modifier of the effect of diesel exhaust exposure on lung cancer risk will be evaluated if numbers permit.

7. BIOMARKER STUDY

7.A Introduction

Several reports reviewing the cancer evidence and potential human risk of diesel exhaust have recently been released.[79-81] These evaluations have all concluded that there is evidence for two mechanisms of cancer induction by diesel exhaust. One mechanism, observed directly in the rat inhalation tumor studies, appears to be due to particle overload, which leads to chronic inflammation and cancer in rats exposed to very fine and ultra fine particles with a high surface area even in the absence of organic

matter. This mechanism is illustrated by the similar tumor response in rats exposed to carbon black particles with a 10X higher surface area than diesel particles but exceedingly low adsorbed organic matter.[82] However, recent work suggests that this mechanism is unlikely to be relevant to humans.[83,84] The second mechanism involves the induction of DNA adducts, mutations, and tumors resulting from the presence of mutagenic polycyclic organic matter adsorbed onto the carbon particles. This mechanism is supported by the tumor induction of the organic matter when administered without the particles in various animal models and the presence of exposure-related DNA adducts in cells from lungs of animals after exposure to diesel exhaust. The recent efforts to develop a scientific database for extrapolating from the animal cancer data to human cancer risk have all documented the need for direct evidence of the effects of diesel exhaust in humans.[80] The need for biomarker studies, including the incorporation of their results in the interpretation of epidemiologic data has been clearly stated,[85] while practical demonstration of their potential has been furnished by the growing number of studies in which they have been employed.[86]

Several small cross-sectional studies have found evidence of increased levels of peripheral white blood cell DNA adducts[87,88] and nitro-PAH urinary metabolites[89] in workers exposed to diesel exhaust. Overall, these have been small studies, and have not measured ambient airborne levels of diesel exhaust for correlation with the biomarker findings. The opportunity to collect biologic samples from this population of high exposed workers would provide a valuable and unique resource to study the association between measured levels of diesel exhaust components in the air and nitro-PAH derived metabolites in urine, macro-molecular adducts in blood, and DNA adducts in exfoliated bronchial and urothelial cells. Evaluation of nitro-PAH DNA adducts in relevant target tissues of exposed humans would provide new information on whether these compounds are biologically active and whether they may be involved in diesel exhaust carcinogenesis. Although the primary focus of this study is on diesel exhaust and lung cancer, it is important to evaluate DNA adducts in several tissues. Evaluation of urothelial cell adducts presents an opportunity to study adducts in another accessible source of epithelial cells for a cancer which might arise from diesel exhaust exposure. Peripheral white blood cell adducts may serve as surrogates for adducts in the lung,[90] and are important to measure since the sensitivity of ^{32}P-postlabeling for nitro-PAH adducts from sputum samples, which are likely to have very low levels of DNA, is uncertain.

In addition, the biomarker study presents an opportunity to evaluate the potential role that inter-individual variation in nitro-PAH activation and detoxification may play in determining the risk of DNA adduct formation. The metabolic enzymes *NAT2* and *P4501A2* play critical roles in the metabolism of nitrogen- containing aromatic compounds, exhibit substantial inter-individual variation, and can be measured following caffeine ingestion.[91]

7.B Study objectives

The main objectives of the biomarker study are as follows:

i) To compare nitro-PAH DNA adduct levels in exfoliated bronchial epithelial cells from sputum samples, in exfoliated urothelial cells from first morning void urine samples, and in white blood cells from peripheral blood samples in the four study groups;

ii) To compare levels of 1-acetylamino-6(8)-hydroxypyrene, the major excreted urinary metabolite of 1-nitropyrene by level of diesel exhaust exposure;

iii) To correlate nitro-PAH metabolite and DNA adduct measurements with personal air monitoring levels of elemental carbon, oxides of nitrogen, and nitro-PAHs.

Results from i) will provide information pertaining to mechanisms of carcinogenicity of diesel exhaust, while the findings from ii) and iii) will demonstrate the extent to which metabolites of important components of diesel exhaust are present in urine, and the degree to which they correlate with exposure levels and individual enzymatic variation.

For this, we propose a cross-sectional study of 50 nonsmoking miners currently exposed to high levels of diesel exhaust with the following comparison groups: 50 smoking miners currently exposed to high levels of diesel exhaust, 30 smoking nonexposed miners and 30 nonsmoking nonexposed miners. Subjects in the three comparison groups will be frequency-matched to the nonsmoking currently exposed miners by mine, age (5-year intervals), race/ethnicity, gender and quantity smoked (in smokers). While we would like to confine the investigation to one mine if possible, additional mines may be needed depending on the degree of cooperation from the workers.

Participation in the study will be strictly voluntary. Exposure to diesel exhaust will be monitored as part of the exposure-assessment component of the study. At the same time, all workers in the most heavily exposed sections of the mine(s) will be contacted. Workers will be asked to provide information on their current usage of tobacco, age, race/ethnicity and gender, and whether or not they would be interested in participating in the study. Similar information will be requested from workers in areas of the mine with no exposure to diesel exhaust.

The field phase of the study will be carried out over a two week period. The study will be explained to potential participants and written informed consent will be obtained. Those in the exposed groups must have worked for at least the previous year in a section of the mine with high exposure to diesel exhaust (to be defined based upon the industrial hygiene data), age greater than 18 years old, and either lifelong non-users of tobacco products or current smokers who have smoked for at least the previous year. Eligibility criteria for the control population will be never having worked in any job with potential for exposure to exhaust from diesel or other combustion engines, and the other criteria described above.

Subjects will be requested to consent to a broad spectrum of biologic assays to be performed on the biologic samples collected. These will include assays currently described in the protocol, and additional assays that may be used to test these samples in the future. Study subjects will be provided with $200 remuneration for participation in the study.

7.C Sample collection

7.C.1 Exposed workers

Samples will be collected over a 5-workday period. One pre-shift urine sample will be collected on day 1. A 125 ml blood sample will be collected on day 5. A first morning, pre-shift, and post-shift urine sample and an induced sputum sample will be collected from each exposed worker on the 4th and 5th day. A one hour urine collection will take place between four and five hours after taking a 100 mg tablet of caffeine on the 5th day of the week. Full-shift personal air monitoring for diesel exhaust components including elemental carbon, oxides of nitrogen, and nitro-PAHs will be performed on each worker on the 3rd, 4th, and 5th days of the work week.

7.C.2 Nonexposed workers

A pre-shift and post-shift urine sample will be collected from each nonexposed worker one time during the work week; on the same day, full-shift personal air monitoring for diesel exhaust components will take place. A first morning void urine sample and an induced sputum sample will be collected from each nonexposed worker on two days during the work week. On one of these occasions a 125 ml blood sample will be collected. A one hour urine collection will take place between four and five hours after taking a 100 mg tablet of caffeine on one day during the work week.

7.C.3 Questionnaire

Upon enrollment, a questionnaire will be administered by trained interviewers to obtain a complete tobacco usage history, recent passive exposure to cigarette smoke, a lifetime occupational history, a detailed history of recent exposure to diesel exhaust and recent use of protective equipment, information on current health status and medicine use, and recent intake of food items that may affect biologic assays. A brief self-administered questionnaire will be used on the two days that each pre- and post- work shift urine sample is collected, obtaining information on exposure to cigarette smoke, medication use, and dietary intake of selected food items within the past 24 hours.

7.C.4 Sample processing

Pre- and post-shift urine samples will be aliquoted and frozen on dry-ice. A 50% glycerol solution will be added to the first morning void urine samples to increase their volume by 20%, and the entire mixture will be frozen on dry-ice. Sputum samples will be collected in a container with 5 ml of 50% glycerin, and frozen on dry ice. Blood sample tubes will be shipped overnight to collaborating laboratories for processing.

7.C.5 Sample analysis

Urine samples will be assayed for 1-acetylamino-6(8)-hydroxypyrene, which is the major excreted urinary metabolite of 1-nitropyrene,[92,93] a representative marker of nitro-PAH, by gas chromatography - mass spectroscopy[94] and for 1-OH-pyrene.[95] Urine samples collected after ingestion of the 100 mg caffeine dose will be analyzed for caffeine metabolites in order to assess the ratios of caffeine metabolites which are influenced by *NAT2* and P4501A2 phenotypes.[91] In addition, they will be assessed for nicotine metabolites to check for current exposure to tobacco.

DNA from exfoliated epithelial cells in urine and sputum samples, and from peripheral white blood cells will be assayed for nitro-PAH and PAH DNA adducts by ^{32}P-postlabeling. DNA adducts have been detected in the lungs of animals exposed to diesel exhaust,[82,96,97] but have yet to be evaluated in heavily exposed humans. The methodology for evaluating DNA adducts in these biologic samples by ^{32}P-postlabeling has been successfully applied to the evaluation of a spectrum of DNA adducts, including aromatic and polycyclic aromatic hydrocarbon compounds (e.g., Talaska et al.[98]; Rothman et al.[99]). DNA adduct standards representing a wide range of nitro-PAH adducts are available for use in these analyses, including DNA adducts formed from 1,6-dinitropyrene, 1,8- dinitropyrene, 6-nitrochrysene, and 1-nitropyrene. Biologic samples will be processed and stored in a manner such that they can be studied for a range of potential assays in the future, including PAH metabolites and adducts, genetic polymorphisms in enzymes that metabolize or detoxify nitro-PAHs (which may act as effect modifiers of the external

exposure-DNA adduct relationship), cytogenetic assays, somatic cell mutation assays, and measures of inflammation and immunologic alterations.

A portion of urine, blood and sputum samples will be pooled to serve as quality control samples. Samples from each pool will be added to the unknown samples (comprising 10% of total samples to be analyzed), and serve as blind quality control replicates.

7.C.6 Data analysis

Analysis of variance will be used to compare both nitro-PAH DNA adduct levels and 1-acetylamino-6(8)-hydroxypyrene levels across the four study groups. The response variables will be normalized with appropriate transformations, as necessary. Group differences will be adjusted for potential confounders, such as diet, exposure to exhaust from other types of combustion engines, and passive exposure to tobacco smoke. For the modeling of nitro-PAH DNA adducts, potential interactions will be evaluated between diesel exhaust exposure and tobacco smoke, and between diesel exhaust exposure and enzyme levels of *NAT2* and *P4501A2*. The latter interactions will also be investigated when modeling the 1-acetylamino-6(8)-hydroxypyrene levels. Dose-response relationships between measures of airborne diesel exhaust and i) 1-acetylamino- 6(8)-hydroxypyrene levels in urine, and ii) nitro-PAH DNA adduct levels in each target site will be evaluated using appropriate regression models.

Power calculations are based upon data published in a recent report of PAH-DNA adduct levels in lymphocytes from nonsmoking garage workers exposed to diesel exhaust.[87] These workers had, on average, 74% higher levels of adducts compared to nonsmoking controls, with standard deviations of 1.26 adducts/10^9 nucleotides in the garage workers and 0.73 adducts/10^9 in the controls. A study of 50 workers exposed to diesel exhaust at levels equal to or greater than levels experienced by these garage workers would have greater than 99% power, at an alpha of 0.05, to detect a 74% increase in PAH-DNA adducts compared to a group of 30 controls.

In addition, substantial experience in biomarker research carried out in populations occupationally exposed to PAHs has shown that a study population of about 40-50 exposed subjects is large enough to detect significant differences in PAH adduct or metabolite levels between exposed and nonexposed workers, and to observe exposure-response relationships between measures of external exposure and biomarker levels.[100-102]

8. EXPOSURE ASSESSMENT

8.A Introduction

Diesel exhaust is a complex mixture of products of combustion, and the composition of the exhaust emission depends on the completeness of the combustion. The major products of the complete combustion of the diesel fuel are carbon dioxide (13%) and water (13%).[2] A small portion of nitrogen is converted to nitrogen oxides and some nitrated hydrocarbons. Incomplete combustion results in the emission of carbon monoxide, unburnt fuel, lubricating oil, and oxidation and nitration products of the fuel and lubricating oil. These incomplete combustion products comprise thousands of chemicals in the gaseous and particulate phases of the diesel exhaust.[3] Because of the complex nature of the diesel exhaust, various surrogates are used to represent overall diesel exhaust exposure. There are two types of surrogates, (1) direct and (2) indirect surrogates used in the assessment of historical exposure to diesel

exhaust. Direct surrogates provide quantitative information on one or more chemical components of the diesel exhaust and are obtained by direct measurements of a particular chemical or classes of chemicals, such as elemental carbon, submicrometer particulates, oxides of nitrogen and carbon, aliphatic and polycyclic aromatic hydrocarbons and their nitrogenated derivatives, and some aldehydes. Indirect surrogates are the current and historical information on the diesel exhaust exposure, such as types and the number of equipment used, the amount of diesel fuel used, ventilation system introduced, production process and other exposure related information.

Previous studies of lung cancer associated with diesel exhaust have typically assessed exposures by dichotomous (exposed/nonexposed) classification without the availability of either direct or indirect surrogates of exposure. Of the 18 cohort studies reviewed in Table 2.1, most used occupation to indicate exposure. Only one of the 18 cohort studies shown in Table 2.1 attempted to measure exposures quantitatively.[37] Another used current industrial hygiene measurements to define jobs where diesel exposure was prevalent.[44] Of the 17 case-control studies reviewed in Table 2.2, only four used quantitative exposure assessments in their analysis or to confirm exposure. A study of Swedish dock workers estimated individual exposures historically by using annual fuel usage at the dock and exposed time data.[66] Gustavsson and colleagues[37] estimated historical exposures by classifying diesel exhaust exposure levels for every employment period. Finally, studies by Steenland et al.[64] and Garshick et al.[58] used current industrial hygiene monitoring to distinguish between jobs with and without diesel exposure.

In this study, we will focus on elemental carbon, submicrometer particulate, and submicrometer combustible dust as the primary surrogates for diesel exhaust, and we will estimate the historical level of these primary surrogates using the results of the current monitoring and the available historical information on other direct surrogates (measurements of other airborne contaminants apart from the primary surrogates) and indirect surrogates (indices of exposure not based on measurement of airborne contaminants, e.g., diesel usage in horsepower) of diesel exhaust exposure. We will conduct an extensive monitoring survey and an exposure data collection program from each operating study mine to establish the relationship between the primary surrogates and the other direct and indirect surrogates of diesel exhaust exposure that were available historically. Based on the information obtained from the current monitoring of the primary surrogates, their correlations with other surrogates, and the employment records, quantitative estimates of historical exposure to the primary surrogates will be derived for each subject in the study. No study published to date has incorporated historical environmental monitoring and other historical exposure data to develop quantitative exposure indices for each study subject. Therefore, this study will provide a stronger base for the evaluation of exposure-response.

8.B Methods

The proposed exposure assessment will utilize either a mine/department/job combination scheme or a homogeneous zone approach depending on which is appropriate for the particular mine and job situation. For jobs that are clearly defined and for which the exposures are relatively constant and not subject to large fluctuations over space or time, the well established mine/department/job approach will be used. For other jobs, the zone approach will be more suitable. For example, the exposures for certain jobs, such as ram car driver, may be fairly uniform from day to day, and personal samples for individuals in those jobs would supply an adequate estimate of the true long-term exposure experienced by those individuals. In contrast, the exposure for a mine manager, who might spend one day in the mine and the rest of the week in an office on the surface, might be best estimated using a zone-based approach. In this

case, time/motion study would reveal the work pattern of the mine manager, and permit an overall exposure to be calculated based on a weighted average of the underground and surface exposure levels. The exposures for the zones in the latter case could be derived by area sampling or by weighted combination of exposure levels measured on jobs within those zones. In the main, we feel that the mine/department/job approach should be adequate for most jobs in most mines. For simplicity, the following exposition refers to the sampling entities, whether jobs or zones, as "uniform exposure categories" (UEC), reflecting the fact that these are distinct units wherein the exposure levels are relatively constant for all workers to whom the units apply.

Figure 8.1 summarizes the steps to be followed in the retrospective assessment of diesel exhaust exposure for the study. The solid lines indicate the main progression of the study, while the dashed lines show how information from one step is employed in other steps.

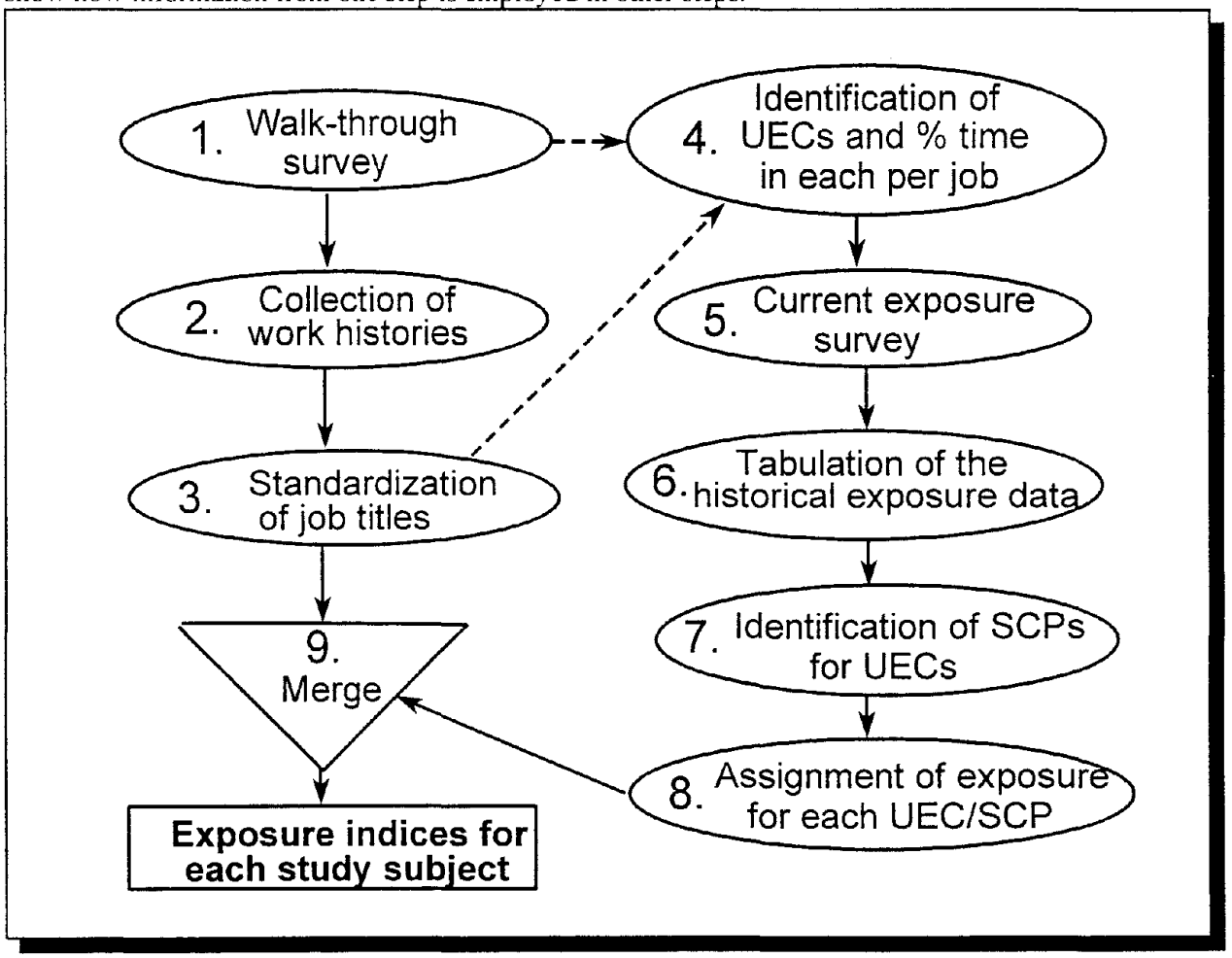

Figure 8.1 Procedural steps of the retrospective assessment of exposure to diesel exhaust

Briefly, work histories of the study subjects will be abstracted from the mine personnel records and standardized. Using information gathered during the mine walk-through surveys and identified from historical data sources, UECs will be identified for each mine.

Exposure surveys will be conducted at each mine in which monitoring for the primary surrogates and other direct surrogates of diesel exhaust exposure will be carried out by job and zone as decided on the basis of the examination of the work histories and consideration of existing exposure data for the mine. In addition, a correlation study will be conducted at each mine to provide relational information between the primary surrogates and the other direct and indirect surrogates of diesel exposure. Historical exposure information will be collected to determine time periods when exposures changed significantly (significant change period = SCP). Assignment of exposure levels for the primary surrogates will be made on the basis of the UEC/SCP combination using all available information on direct and indirect surrogates of diesel exhaust exposure. Exposure indices, such as cumulative exposure, average intensity, time weighted cumulative exposure, metabolically saturated exposure intensity, peak exposure, and overall summary indices for the primary surrogates will be calculated for each study subject by merging the subjects' work histories with the exposure assignments for the UEC/SCP combination. In addition, similar exposure indices will be derived for certain of the secondary surrogates (e.g., NO_2), together with some cruder surrogates, such as total tenure underground, tenure at the face, etc.

A sensitivity analysis will be undertaken to determine the effect of varying the critical parameters of the exposure assessment process on the derived exposures.

8.C Exposure assessment for the cohort study

The following nine steps detail the retrospective exposure assessment procedures that will be used for the cohort study.

8.C.1 Mine walk-through surveys

A walk-through survey will be held at each mine. The purpose of the walk-through survey is to assess the mine for the purpose of planning the main IH survey. At the walk-through survey, NIOSH and NCI staff will meet with mine personnel in order to review the mine organization, history, layout, and spatial and temporal patterns of ventilation, diesel usage, fuel consumption and exposure levels. Records will be collected on job classifications, numbers of workers, mine plan, and other factors of relevance in planning the main IH survey. Particular emphasis will be placed on ascertaining information pertinent to identifying UECs.

8.C.2 Collection of work histories

Personnel records will be microfilmed at the mine site, abstracted, and pertinent information entered into the MDS. The MDS will be used to assemble the cohort and will include work history information such as job title, work area, and start and stop dates for each assigned job during the workers' tenure at the mine (see Section 5 for details).

8.C.3 Standardization of job titles

To maximize the exposure-specific information, standardized mine-specific job title codes will be assigned for each job in the work history. First, lists of reported occupations will be tabulated for each mine. The standardization process will start with spelling and word order of jobs. For example, "crusher op" will be standardized to crusher operator. On the other hand, primary crusher operator and secondary crusher operator will be two different jobs. In addition, professional judgement by the industrial

hygienist may be used to aggregate certain jobs with the same tasks but different names. For instance if, within the same mine, one job history has loader operator and another has LHD operator, the industrial hygienist will determine whether these jobs are the same or different. As an aid in standardizing the job and department titles and in designing the current exposure survey, currently available information on work histories and jobs from the feasibility study, prior morbidity studies, prior IH surveys, and the walk-through surveys will be tabulated to determine the distributions of miners by job for each mine.

8.C.4 Identification of UECs and percentage time spent in each UEC per job

For the purpose of exposure assessment UECs will be defined. A UEC is an entity in which all workers have a similar range of exposure levels to diesel exhaust particulate. UECs can be either specific jobs or certain zones of the mine. Jobs with fairly constant uniform exposures will comprise individual UECs. For jobs which are not clearly defined or for which exposures are heavily dependent on task or location, exposure levels will be assigned using a weighted average of zone-based UECs. IH data from the walk-through survey, from the 1976 MSHA study, and from other sources will be consulted in the definition of UECs.

In order to properly quantify diesel exposures, we will estimate the average time spent in each UEC for each standardized job title. For UECs which are themselves jobs, the time allocation is obviously 100%. In other cases, typical movement of jobs between zones will be assessed along with the length of time spent in each zone. This will be done by observation and by interview of miners and mine personnel. The information will be used to create a UEC/job dictionary that will be used to determine the percent time spent in each zone during each significant change time period for each standardized job title. Table 8.1 shows what a UEC/SCP job dictionary might look like for one zone-based job.

SCP	Job Titles	Work Pattern		
		Production	Development	Office
1962-1966	Surveyor	25%	25%	50%

Table 8.1 Example of part of a UEC/job dictionary

Each job identified will be examined carefully to see if its specification is sufficiently clear, and its exposure uniform enough, for it to be defined as a single UEC (or in combination with like jobs as a UEC), or whether its exposure is best ascertained using a zone approach. Information gained from this activity will provide the basis for the sampling strategy described next.

8.C.5 Current exposure survey

We will conduct at least one comprehensive industrial hygiene (IH) survey in both the underground and the surface operations in each active mine in the study. The purpose of this IH survey is to monitor current levels of the primary and other direct surrogates of diesel exhaust exposure and to obtain historical information on direct and indirect surrogates of diesel exhaust exposure. The information to be collected in the surveys will be used in the retrospective assessment of exposure to elemental carbon. An operating manual will be developed for the conduct of the IH surveys.

The sampling plan will measure the primary surrogates and other direct surrogates for the majority of occupations and for various zones throughout the working areas in both the underground and surface sections of the mine and mill. Information from the activities described in Sections 8.C.1 - 8.C.4 will provide the rationale for which jobs and zones to sample. The underground area will have more intensive sampling than the surface area, because there are more potentially exposed employees working underground and exposures are generally higher and more variable. Jobs will be assessed using multiple personal samples. Underground sampling zones may include one or more of the following areas: Shaft (Intake), Main Haulage, Maintenance - Diesel, Shop Areas - Other, Crusher/Mill, Dump Sites or Feeder/Breaker, Ore Haulage, Drilling/Roof Bolting, Continuous Miner/LHD/Other Production, Beltline, Section - General Work Areas, Break Area, and Non-work Area (Mine Average). Zones on the surface may include office areas, diesel maintenance areas, other areas with diesel exposure, and areas without diesel exposure.

The aim is to collect duplicate samples for each UEC for at least five production shifts during which normal mining operations are observed for underground operations and for at least two normal shifts for surface operations. This will yield a minimum of ten samples of each surrogate in every underground UEC and four samples in every surface UEC. We intend to relate the intensity of sampling to the expected variability in diesel exhaust concentration and to the number of workers for whom the results would apply.

8.C.5.a Sampling for the surrogates of diesel exhaust exposure

The following samples will be taken to assess the surrogates of diesel exhaust exposure:

i) Primary surrogates - Elemental carbon (EC) was chosen based on the findings of Fowler,[103] where it was found to be the best indicator of "diesel exhaust as an entity." A more recent assessment has also defined it as the most appropriate surrogate of diesel particulate in the occupational setting.[104] Among the carbon analysis methods used by participants in the Carbonaceous Species Methods Comparison Study in Glendora, CA,[105] the thermal-optical method was chosen by NIOSH researchers for measuring diesel exposure in the Teamster's IH study, because it was recommended by a number of the study's participants (including Lawrence Berkeley Laboratory and General Motors Inc.),[106] and it was commercially available. An advantage of the thermal-optical method of carbon analysis is that it measures total carbon by separately analyzing and quantifying both the elemental and the organic portions of the diesel exhaust particulate. Tests indicate that approximately 1 - 2% of the total carbon (elemental plus organic carbon) is elemental carbon contributed by tobacco smoke.[3,107] In the mining environment, the elemental carbon analysis measures diesel soot almost exclusively, since use of explosives in the mining process (conventional mining) would not significantly alter the EC levels. The organic portion of the total carbon particulate includes contaminants other than diesel exhaust. Oil mists are one example of a compound that would be measured by the organic carbon result from the thermal-optical method. EC analysis has recently been approved as NIOSH Analytical Method 5040, and has been chosen by the German government as the index of choice for regulation of diesel exhaust levels. Appendix D gives information on the precision of the EC method. Further information on the method can be found in publications by Birch and Cary.[107,108]

The two other primary surrogates of diesel exhaust to be used in this study are submicrometer combustible dust (SCD), and submicrometer particulate (SP). Both indices focus on the small particulate (< 1 μm) which forms the major constituent of diesel exhaust. SP is the basis for a proposed new ACGIH TLV for diesel exhaust.[109]

ii) Other direct surrogates of diesel exhaust exposure - In addition to the primary surrogates listed in i) above, respirable particulate, total particulate, nitro-PAH, CO, CO_2, SO_2, NO, and NO_2 will be measured in the area sampling packages. Each of these contaminants, together with indirect surrogates, will be used alone, and in combination, to develop a variety of estimators of elemental carbon exposure. All reflect to some extent level of exposure to diesel exhaust, and will be used in a correlation study (see Section 8.C.5.c) in order to extrapolate past levels of exposure to elemental carbon.

8.C.5.b Sampling for other airborne contaminants

As a precautionary measure, measurements of the following potential confounders will be undertaken as follows:

i) Radon - Sampling for radon will be conducted one time at each area sampling location to confirm the reported low levels of radon exposure.

ii) Metals - Airborne samples for known or suspected carcinogenic metals (such as chromium, arsenic and nickel), will be collected to confirm the absence of these metals on one sampling shift at each area sampling location.

iii) Free silica - To confirm the low level of silica exposures, bulk and airborne silica samples will be collected from each area sampling location during one shift, and one bulk sample will be collected at the face.

iv) Asbestos - Samples will be collected in both the mine and the mill areas to measure the concentration of airborne asbestos. Settled dust samples will also be collected in both the mine and the mill. Multiple samples will be collected in areas where it appears that asbestos has been used as a building material.

8.C.5.c Correlation between elemental carbon and other direct and indirect surrogates of diesel exhaust exposure

During the industrial hygiene survey, we will monitor the level of the primary and other surrogates of diesel exhaust exposure in various locations at each mine. Mine-specific and overall correlation coefficients will be estimated for all of the direct surrogates measured during the surveys, and relationships between them developed and examined. A priority index will be assigned to each direct and indirect surrogate based upon its relationship with the other surrogates, taking into account the strength of the relationship and other factors. This priority index will be used in the selection of available surrogates in estimating historical exposures to the primary surrogates.

Appendix E provides information on levels of elemental carbon and other primary surrogates at the mine in Phase II of the feasibility study. The appendix also gives details of the correlation between elemental carbon and other direct surrogates of diesel exhaust exposure.

8.C.6 Tabulation of the historic exposure data

8.C.6.a Historic monitoring data on direct surrogates of diesel exposure

Historic monitoring data from NIOSH, MSHA, the Bureau of Mines (BOM), and companies will be acquired where possible. The main historical non-compliance dataset pertains to IH surveys conducted by the then Mine Enforcement and Safety Agency (MESA) in 1976. In these surveys MESA personnel spent several weeks at each mine making a thorough characterization of the mine environment. The surveys included thousands of personal and area samples of NO_2 and other compounds associated with diesel usage, as well as many dust concentration measurements. They were undertaken with the objective of providing a valid exposure database sufficient for reliable estimation of individual worker exposures to the dust and diesel exhaust components of the airborne ventilation, with the ultimate aim of correlating these derived exposure estimates with measures of respiratory morbidity, including ventilatory function and chest symptoms. In addition to this non-compliance database, MSHA compliance sampling from the MIDAS database (1973 to the present) and other MSHA and NIOSH records will be obtained.

A detailed summary of the data from the 1976 IH surveys is presented in Appendix F.

8.C.6.b Historical information on indirect surrogates of diesel exposure

Because availability of the historical monitoring data are limited to only certain years, additional diesel-related information will be necessary to develop fully informative models. Therefore, the following exposure-related information on indirect surrogates will be obtained, where possible, from each mine for current and past conditions to assess exposure for the time periods when no monitoring data are available:

i) The number, type, and horsepower of pieces of diesel equipment in use by shift and day.
ii) Ventilation - Total mine and working area
iii) Production by shift and day
iv) Diesel fuel usage
v) Mine dimensions (roof height, entry width, etc.)
vi) Required personal protective equipment usage.

Much of this information will be collected during the initial walk-through survey. It will first be used to define UECs for the main IH survey. It will also be used to derive factors for extrapolation from known levels to unknown levels in other time periods (see Sections 8.C.7 and 8.C.8 following).

8.C.7 Identification of significant change periods for UECs

Since exposure levels will have changed over the study period, the estimation process must take time period into account. Estimates are often made by year, but to maximize the precision of estimation and to increase efficiency, years will be collapsed on the basis of evidence suggesting that exposure levels

within a time period were unchanged.[110] Important changes in diesel exhaust exposure during different time periods will be assessed by evaluating information collected on the direct and indirect surrogates listed in 8.C.6.

The time categories in the UEC/SCP exposure profile will reflect important changes in production, equipment, or other factors that could have caused a change in exposure during a specific time. For example: In 1960, a mine bought three pieces of diesel equipment. In 1965, the mine doubled its ventilation. In 1966, the mine bought 20 pieces of diesel equipment. In this case, the first significant change period for applicable work areas in the matrix would be from 1960 - 1965. The second would be from 1965 - 1966. The third significant change period would run from 1966, and so on.

8.C.8 Assignment of exposure for each UEC/SCP

Exposure profiles will be developed for each mine in order to estimate exposure levels for each job within department within mine combination. Each of these combinations will be identified as an "exposure cell" or "cell".

Development of the exposure profile and the estimation of the historical exposures will be completed using a computerized data management system similar to one developed by the National Cancer Institute[111] that provides a systematic organization of the exposure information collected from various sources at each site.

This program leads the researcher through a variety of steps in order to build a complete exposure assessment. The steps (with modifications specific to this project) are described in the following:

> **i) Baseline estimates** - At least one UEC/SCP baseline estimate will be the starting point for reconstructing exposure levels for historical periods for which virtually no measurements exist. All current monitoring results will be used as baseline estimates for each UEC for the most recent significant change period. In addition, historical monitoring data with a geometric standard deviation of 5 or less will be used in the determination of additional baseline estimates.
>
> **ii) Completing the job matrix** - Once all UECs have at least one baseline estimate, the next step is to complete the assessment by developing estimates for the cells with little or no data. Estimated exposures will be based upon the effect of significant changes on the baseline estimates in the mining environment. The effect can be estimated using monitoring data, estimates of similar uniform exposure categories or significant change periods, linear regression, if applicable, and/or professional judgement. The priority index of each surrogate will determine which available surrogate information will be used in estimating quantitative exposure level of elemental carbon for each cell.

8.C.9 Merging of estimates of exposure and work histories

After completion of the UEC/SCP exposure matrix, it will be merged with the UEC/job dictionary. This will result in quantitative exposures for each job by significant change period. This matrix will be merged with the job history data to calculate exposure indices, such as cumulative exposure, average intensity, time-weighted cumulative exposure, metabolically saturated exposure level, peak exposure, and combined diesel exposure for each study subject. Tables 8.2 - 8.4 exemplify how an exposure estimate

for an individual will be derived. This individual is assumed to have worked from 1974 - 1978 in job #1, and from 1979 - 1982 in job #2. First, Table 8.2 gives the individual's jobs, and how they break down by time in various UECs. Next, Table 8.3 shows the exposures for each SCP for each zone. Finally, Table 8.4 shows how the information in Tables 8.2 and 8.3 is used to derive the exposure estimate for the individual.

Work history jobs	**Begin Date**	**End Date**	**Zone or job based**	**Relevant UECs**	**% time**
Job #1	1974	1978	Zone	UEC#1	60%
				UEC#2	20%
				UEC#9	20%
Job #2	1979	1982	Job	UEC#15 = job 22	100%

Table 8.2 Example of an individual work history file

UECs	**Significant Changes (calendar time periods)**				
	1960	**1970**		**1980**	**1990**
UEC#1	10 ppm	7 ppm		5 ppm	3 ppm
UEC#2	20 ppm	16 ppm	12 ppm	8 ppm	6 ppm
-------	----------				
UEC#9	no diesel exposure	4 ppm	2 ppm	1 ppm	
-------	----------				
UEC#15	9 ppm		8 ppm	5 ppm	

Table 8.3 Example of an UEC/SCP-exposure matrix (exposure file)

Cumulative exposure:
Job #1: ((7 ppm * 0.6) + (12 ppm * 0.2) + (4 ppm * 0.2)) * (4 years) = 30 ppm-year
Job #2: (8 ppm) * (1 year) + (5 ppm) * (2 years) = 18 ppm-year
Complete work history exposure = 29.6 + 18.0 = 48 ppm-year

Average intensity:
(48 ppm-year) / (7 years of exposure) = 6.8 ppm

Table 8.4 Calculation of two exposure indices for the individual based on Tables 8.2 and 8.3. (Figures rounded to two significant figures to reflect uncertainty)

8.D Additional procedures for the nested case-control study

In addition to the IH data collected for the cohort study, we will attempt to collect and employ more detailed subject-specific historical information for the case-control study (e.g., individual use of diesel equipment, effects of ventilation, use of personal protective equipment, work practices, and other factors that affect exposure). This is possible because the number of subjects in the case-control study is smaller and more manageable than that in the cohort study. A special subject-specific exposure abstraction form and questionnaire will be developed to gather the relevant historical exposure information. The abstraction form will be filled out at the mine site with a team of co-workers, supervisors, safety officers, and long-term employees to reconstruct the subject's historical working environment. The subject-specific exposure information gained during interview and elsewhere will enhance that described previously, leading to superior knowledge of individual worker exposure. In particular, it may be possible to refine estimates of exposure experienced prior to work at the study mines using information from the questionnaire and elsewhere.

8.E Exposure assessment for the biomarker study

The biomarker study provides us with the opportunity to collect biologic samples from a population that is heavily exposed to diesel exhaust particulate (see Section 7). On the day when urine specimens are collected, and the three previous days, each participant will have their personal exposures to elemental carbon and the oxides of nitrogen measured over a full eight-hour shift. In addition to the personal samples, the direct surrogates of diesel exhaust noted in Section 8.C.5.a will be monitored in the subjects' UECs using area stations. If feasible, additional exposure data will be collected during the several months prior to biologic sample collection.

A study will be conducted of the association between the internal (e.g., urinary nitro-PAH metabolites) and the external (e.g., elemental carbon, submicrometer particulate and nitro-PAHs in the air) measures of diesel exhaust exposure. These results will also help us to determine the optimum exposure surrogate for the diesel exposure.

9. QUALITY CONTROL

9.A Cohort study

Records identified as pertinent to the study during site and off-site visits will be microfilmed. At NIOSH, Morgantown, the records on these films will be abstracted and entered into a computer database independently by two clerks. The agreement between the two transcriptions will be checked, and disagreements resolved by the supervisor. Information entered will be subjected to logical and consistency checks (such as consecutive job start and finish dates agreeing, birth dates and first job start dates being reasonable, etc). Where possible, the identified cohort will be matched against Social Security Administration quarterly earnings records to ensure completeness.

The follow-up procedures are designed to ensure that information on vital status is complete and reliable. They include obtaining information from various sources, primarily the National Death Index and Social Security, as well as the IRS. Confirmation of vital status will be obtained by contacting Postmasters. Special efforts will be made for hard-to-locate and doubtful cases.

9.B Case-control study

Standardized procedures will be used to elicit information from next of kin of cases and dead controls, and from living controls. The interviewers will be trained in standardized interviewing techniques and will be provided with a manual detailing all procedures, including methods to deal with ambiguous and unclear responses and to obtain information accurately in an unbiased fashion. Every effort will be made to blind the interviewers to the case-control status. The information obtained from interviews will be coded independently and separately keypunched and verified. The supervisor will re-interview a 10% random sample of subjects to validate responses to the interview.

The diagnosis of lung cancer will be histologically confirmed, where possible, by examination of pathology slides by an experienced pathologist.

9.C Biomarker study

Quality control samples will be created for all analyses performed on urine, blood and sputum samples. Ten per cent of each biologic sample collected from study subjects will be used to make quality control pools for urine, blood and sputum. Replicate samples will be made from each pool. One quality control replicate will be added to every batch of nine study subject samples. Quality control samples will be labeled and stored in tubes such that they will be indistinguishable from study subject samples. Analytic results from the quality control replicate samples will enable us to calculate a coefficient of variation for each assay.

9.D Exposure assessment

Double instrumentation will be used to collect samples, avoiding loss of data due to sampler failure and providing more reliable estimates of exposures. Standard NIOSH laboratory analytical procedures (including blanks and spiked samples) will be used for sampling and analysis in order to provide reliable and accurate measurements. Derivation of exposure estimates will be made blinded to the vital status or case-control status of individuals. Finally, a sensitivity analysis will be undertaken in order to determine the effect on the mortality findings of variations in the major parameters used in the development of retrospective exposures.

10. LEGAL AUTHORITY

NIOSH's authority for collecting the information described in this study is provided by the Federal Mine Safety and Health Act of 1969 (30 U.S.C 801 et seq.) And NIOSH regulations 42 C.F.R. Part 85a.

11. WORKER NOTIFICATION

Findings from the complete study will be communicated to workers following the standard procedures as described in the NIOSH 'Worker Notification Procedures Manual'. These include:

i) a final study report will be sent to each of the study mines, to interested mining organizations, to all the unions involved, and to relevant governmental institutions.

ii) the decision to send individual worker notification letters will be based on the strength of the evidence for increased risk of disease. This will be decided upon based on the guidelines described in the worker notification manual.

Since the nested case-control and biomarker components of the study are considered active participation studies, individual notification of study results will be sent to study participants.

12. INVESTIGATORS (Alphabetical order)

This study will be a collaborative effort between NCI and NIOSH. The Environmental Protection Agency will collaborate on the biomarker component of the study. A highly qualified multi-disciplinary team of epidemiologists, statisticians, industrial hygienists, toxicologists, and clinicians has been established.

12.A Project Officers

Dr. Michael Attfield -- Dr. Attfield is an epidemiologist with the Epidemiological Investigations Branch at the Division of Respiratory Disease Studies, NIOSH, at Morgantown, WV. He has 27 years experience in undertaking major epidemiologic studies of health effects in underground miners, including several studies of the relationship between diesel exhaust exposure and lung disease. Dr. Attfield will serve as Co-Project Officer, and be responsible for overseeing the scientific and administrative aspects of the study.

Dr. Debra Silverman -- Dr. Silverman is an epidemiologist with a Sc.D. in epidemiology and a Sc.M. in biostatistics. She has 24 years of experience conducting epidemiologic studies of cancer at NCI. She is an expert on the carcinogenicity of diesel exhaust and has conducted several major studies of diesel exhaust exposure and cancer. Dr. Silverman will serve as Co-Project Officer overseeing the scientific and administrative aspects of the study and will be the lead researcher on the nested case-control study of lung cancer.

12.B Other investigators

Dr. Jean Cox-Ganser -- Dr. Cox-Ganser is a statistician with the Epidemiological Investigations Branch at the Division of Respiratory Disease Studies, NIOSH, in Morgantown, WV. Before coming to NIOSH, she trained as a biologist and was a project leader at the Pollution Research Group at the University of Natal, RSA. She later qualified as a statistician and worked at the Department of Community Medicine, West Virginia University. Dr. Cox-Ganser will be the lead researcher for the cohort mortality component of this study.

Dr. Mustafa Dosemeci -- Dr. Dosemeci is an industrial hygienist with a Ph.D. in occupational health. He has eleven years experience conducting studies of occupational exposure and cancer risk at NCI. He is an expert on retrospective exposure assessment, a key methodology to be in employed in this study. Dr. Dosemeci will be responsible for the methodologic aspects of the study pertaining to the retrospective exposure assessment.

Dr. Joellen Lewtas -- Dr. Lewtas is a Ph.D biochemist in the U.S. Environmental Protection Agency, and an expert in the area of cancer biomarkers, including analysis of DNA adducts in various human cell lines. She will be working on the biomarker study.

Dr. Tong-man Ong -- Dr. Ong has a Ph.D in genetics and has worked at Oak Ridge National Laboratory and as a geneticist at the National Institute of Environmental Health Sciences. Currently, he is a research biologist in genetic toxicology research at NIOSH. He has specialized in the area of chemical mutagenesis and genetic monitoring of workers, and has published widely in this area. He will be working on the biomarker study.

Dr. Nathaniel Rothman -- Dr. Rothman is an epidemiologist at NCI. He is an occupational physician with a MPH in occupational health and a MHS in occupational and environmental epidemiology. He is an expert on incorporating biologic markers of exposure, early biologic effects and susceptibility into epidemiologic studies of environmental and occupational causes of cancer. He has nine years of experience in this area. He will be responsible for the biomarker component of the study.

Rebecca Stanevich, MPH, MS -- Ms. Stanevich is an Occupational Health Specialist with expertise in industrial hygiene. occupational health nursing, safety, and epidemiology. She was the NIOSH project officer on the feasibility study. She has 20 years experience with NIOSH on a large variety of projects. Ms. Stanevich will be responsible for the industrial hygiene surveys and exposure assessment aspects of the study.

13. BUDGET

Tables 13.1 and 13.2 give details of the budgeted costs for the project. The first provides information on funds allocated to the NCI/NIOSH Interagency Agreement, while the second lists other expenditures.

Table 13.1 Study expenses included under the NCI/NIOSH interagency agreement	
YEAR 1	
Copy personnel records	$87,500
Data entry of personnel records	$297,500
Air Samples for Nitro-PAH	$50,000
Elemental Carbon Analysis	$50,000
Total	**$485,000**
YEAR 2	
Copy personnel records	$67,500
Data entry of personnel records	$392,500
Elemental Carbon Analysis	$25,000
Collection of biologic samples from cross-sectional study	$100,000
Total	**$585,000**
YEAR 3	
Post Office Tracing	$2,000
NDI	$35,000
Procure Death Certificates	$10,000
Code Death Certificates	$8,000
Data entry of death certs & codes	$10,000
Analyses of urine samples for 1-nitropyrene metabolite	$40,000
Locate controls and next-of-kin	$10,000
Interviews and data entry	$35,000
Total	**$150,000**
YEARS 4 - 6	
No expenses	$0
Total	**$0**
STUDY TOTAL	**$1,220,000**

Table 13.2 Additional expenses not funded by the NCI/NIOSH interagency agreement		
	NCI	**NIOSH**
Pathology Review (Including material retrieval)		
Approx . 160 @ $50 each		$8,000.00
Travel		
Travel to mines	$14,400.00	$110,875.00
Pittsburgh conference	$1,600.00	$1,000.00
Other		$16,000.00
Equipment		
Biologic sample supplies/shipping	$25,000.00	
IH equipment and supplies		$75,700.00
Other equipment and supplies		$11,400.00
Laboratory analysis of biologic specimens	$250,000.00	
Data analysis		
Computer support contract	$20,000.00	$15,000.00
Computers and software		$15,000.00
Total	**$311,000.00**	**$253,875.00**

14. TIME SCHEDULE

The study is projected to take six years following start of data collection. The various activities have been scheduled to occur in the order shown below, though actual progress will be influenced by circumstances encountered during the course of the project.

Year 1

Initiate OMB and IRB clearances.
Begin microfilming personnel records at off-site location and mines.
Begin coding and entering data.
Initiate industrial hygiene surveys at mine sites.
Begin mortality follow-up.
Begin acquiring death certificates, and coding and keypunching.

Year 2

Complete microfilming at mines and off-site locations.
Complete IH surveys.
Complete coding and entering of personal and IH data.
Start to identify cases, to select controls, and to conduct case-control interviews.

Complete collection of biologic samples and corresponding IH samples

Year 3

Complete mortality follow-up.
Complete acquisition of death certificates, and their coding and data entry.
Complete identification of cases, selection of controls, and case-control interviews.

Year 4

Complete quantitative assessment of worker exposures.
Complete biomarker study.

Year 5

Complete Phase I cohort study analysis.
Complete Phase I case-control analysis.

Year 6

Complete Phase II cohort study analysis.
Complete Phase II case-control analysis.
Complete worker notification.

15. IRB APPROVALS

Institutional Review Board approvals for the conduct of the study will be obtained from the NCI IRB and the NIOSH HSRB.

16. PUBLICATIONS

Draft reports will be sent to the study companies and labor unions for review of technical accuracy and trade secrets (companies only).

Reports from this study will include the Phase I and II mortality analyses of the cohort study and the nested case-control study. Since the Phase I cohort and case-control reports will be complementary, NIOSH/NCI intend to submit them to the same journal for concurrent publication. The same procedure will apply to the Phase II reports. Other important publications will arise from the results of the exposure assessment phase of the project, and the biomarker study. In addition, there will be other publications relating to subsidiary aspects of the study, and arising from methodological issues. The collaborative effort between NCI and NIOSH will lead to joint authorship on all presentations, published papers, and reports (with joint agreement by NCI and NIOSH on any proposed exceptions to this rule). Papers involving the biomarker component will also include authorship by collaborators from EPA. Members of the study research team wishing to prepare publications and presentations will seek concurrence from the team before proceeding. Authorship on the respective publications and presentations will be determined based on standard scientific procedures, reflecting the level of contribution to the research and resulting report.

No personal identifiers will be included in any of the manuscripts, presentations, or reports arising from the study.

17. PROJECT AGREEMENT

The undersigned, the co-project officers and other representatives of their agencies, have read and approved the study protocol dated June 4, 1997 as the plan to carry out this study, with the understanding that the protocol is subject to changes as deemed necessary during the course of the study. Any changes to this plan must be approved by these individuals.

Michael Attfield, Ph.D.,
National Institute for Occupational Safety and Health

Kathleen Kreiss, M.D.,
National Institute for Occupational Safety and Health

Debra Silverman, Sc.D., National Cancer Institute

Aaron Blair, Ph.D., National Cancer Institute

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APPENDIX A - BASIC INFORMATION ON MINES IN THE FEASIBILITY STUDY

MINE #	COMMODITY	STATE	ACTIVE 1994	YR. DIESEL	# EMP. 1978 (MSHA)	# EMP. 1992 (MSHA)	% EMP. UNDER-GROUND (1992, FEASIBILITY STUDY)
1	LIMESTONE	VA	YES	1948	114	97	25
2	LIME	VA	YES	1948	140	131	33
3	LIMESTONE	WV	YES	1950	81	84	60
4	GYPSUM	IN	YES	1955	42	191	20
5	LIMESTONE	KY	YES	1964	69	178	39
6	TRONA	WY	YES	1967	1200	670	49
7	TRONA	WY	YES	1962	528	540	36
8	TRONA	WY	YES	1965	1248	1189	34
9	TRONA	WY	YES	1970	200	309	44
10	SALT	NY	NO	1960	250	227	55
11	SALT	NY	YES	1970	110	157	55
12	SALT	OH	YES	1963	184	203	64
13	SALT	OH	YES	1960	249	203	61
14	LIMESTONE	IL	YES	1950	46	53	30
15	LIME	MO	YES	1960	775	856	21
16	POTASH	NM	YES	1964	300	300	46
17	POTASH	NM	YES	1950	92	183	53
18	POTASH	NM	NO	1952	269	424	49
19	POTASH	NM	YES	1964	80	186	49
20	POTASH	NM	YES	1965	269	390	60
21	POTASH	NM	YES	1950	237	584	41
22	SALT	LA	YES	1965	104	131	72
23	SALT	LA	YES	1962	73	204	55
24	SALT	LA	YES	1950	97	284	45

Table A.1 Information on the 24 non-metal mines included in the feasibility study

APPENDIX B - MINE SELECTION

This study is limited to non-metal mines with documented low levels of exposure to certain potential lung carcinogens, i.e., radon, arsenic, asbestos, and silica. Information pertinent to selection of candidate mines was gathered on the 24 non-metal mines during Phase I of the feasibility study, and supplemented by Mine Safety and Health Administration (MSHA) compliance data and historical exposure databases. During this phase of the feasibility study, site visits were made to estimate the total number of personnel files kept by the mine and to microfilm a random sample of between 10 to 15 percent of the personnel files. A NIOSH industrial hygienist made a walk-through of each facility, and inquired into past and present operations of the mine with particular attention to the use of diesel equipment.

The following factors formed the primary basis of the mine selection:

i) Expected numbers of deaths from lung cancer at the mine. This figure was derived from the personnel records abstracted during the feasibility study.

ii) Extent and duration of exposure to diesel exhaust at the mine. This information was gained from historical and current data on exposures and on diesel equipment usage and fuel consumption.

iii) Availability of historical exposure information. Inclusion in the 1976-78 NIOSH/MSHA study was heavily weighted in the mine selection process. In addition, current operating status was also a factor, because of the desirability of a current exposure assessment.

iv) Quality of personnel records (obtained by examination and edit of records obtained during the feasibility study).

In addition, it was decided that we would try not to include two mines from the same company, if doing so would have minimal impact on the scientific quality of the study.

B.1 Expected number of lung cancer deaths

For each of the 24 mines visited, an estimate was made of the expected number of lung cancer deaths for the eligible workers, based on Monson's U.S. white male 8th revision death rates, adjusted for deaths from all other causes. In summary this was achieved as follows.

1) The proportion of eligible workers was estimated from each mine's sample of records and used to estimate the total number of eligible workers in the mines record systems.

2) Resampling was then used on the eligible samples to boost the number of observations for each mine to these calculated totals.

3) The final data sets for each of the 24 mines was entered into a modified life table analysis system 'OCMAP' to obtain person years and expected number of lung cancer deaths as well as expected number of deaths due to all causes for strata defined on age and calendar time categories.

4) A QUATTRO PRO spreadsheet program was used to obtain estimates of numbers of expected lung cancer deaths corrected for deaths due to other causes.

B.2 Diesel exhaust exposure data

The availability of considerable historical monitoring data is an advantage of this study, and has played a strong role in the selection of mines for the full study from the 24 mines visited during the feasibility study. These data are needed for the development of historical exposure estimates. Of these 24 mines, eight were included in a 1976-78 survey of metal/non-metal mines conducted by the Bureau of Mines, MSHA and NIOSH. During this 1976-1978 survey, area and personal samples for NO_2, total dust, respirable dust, radon, arsenic, silica and other mine contaminants were taken. All 24 mines have some MSHA compliance data available in the MIDAS database from 1973 to the present on many different contaminants, including those mentioned above. Additional exposure data available at these mines include number of pieces of diesel equipment used over the years, horsepower ratings, and diesel fuel consumed over the period of interest.

A subjective evaluation of the levels of diesel exhaust exposure underground in the 24 mines was made using data on NO_2 levels in the 24 mines from both the 1976-1978 survey reports and the MSHA MIDAS database, as well as a Bureau of Mines report.[112] These values together with information, where available, on numbers of pieces of diesel equipment used in the mines over the years since diesel use was introduced, were used to decide on adequacy of diesel exhaust exposure for inclusion of the mine in the study. A score of 1 - 3 was assigned on the basis of the estimated level of exposure. (Note that this score is intended to reflect the relative level of diesel exhaust underground across mines. At any mine, a substantial gradient of exposure is expected to exist between underground and surface occupations.)

B.3 Quality of personnel records

A number of factors were taken into consideration concerning the quality of personnel records:

1) availability of records over the entire period of follow-up;
2) existence of demographic data including gender, race, social security number and date of birth;
3) existence of next of kin data;
4) existence of prior work-histories, as are usually found on job application forms;
5) existence of department and job titles that were good indications of tasks and where the employee worked; and
6) completeness of start and stop dates for the jobs held at the mine.

Information from the feasibility study site visits was used to evaluate the adequacy of records for each of the 24 mines using these criteria. A score from 1 to 3 was allocated to each mine on the basis of this evaluation (3=better, 1=worse).

Table B.1 below, gives information on the above factors.

Mine ID number	In 1976 study	Expected number of LC deaths	Exposure level	Record quality	Mine open currently	In same company († & ✶)
1		1.5	1	1	✔	
2		0.3*	1	3	✔	
3		3.7	2	1	✔	
4		2.9	2	3	✔	
5		11.5*	2	1	✔	
6	✔	17.2	1	3	✔	
7		15.7	1	3	✔	
8	✔	8.4	2	3	✔	
9		1.4	1	3	✔	
10		10.6	2	3		
11		2.5	1	3	✔	
12		2.5	3	3	✔	†
13	✔	5.3	2	2	✔	✶
14		0.7	2	3	✔	
15		38.6	3	2	✔	
16	✔	2.2*	3	3	✔	
17		4.3*	1	3	✔	
18	✔	5.0*	3	3		
19	✔	4.4*	3	3	✔	
20	✔	83.8	1	3	✔	
21	✔	15.1	3	2	✔	
22		1.4	3	2	✔	
23		7.9	3	3	✔	†
24		14.9	2	1	✔	✶

* indicates probable underestimate because of inability to sample certain records during feasibility study.

Table B.1 Information from feasibility study and elsewhere used to rank mines

On the basis of the information in Table B.1 the groups of mines were identified and placed into priority categories according to their usefulness to the study (Table B.2). (Note that mines 2 and 16 - 19 were considered to be larger mines because of the likely underestimation of lung cases at those mines.)

Mine numbers in approximate priority order	Comment
21 8 19 16 18 13	Had to have 1976 data ***and*** be currently open, are larger mines, have good to moderate quality records, and have high to moderate exposures.
15 23 6 7	Had to have 1976 data ***or*** be currently open, are larger mines, have good to moderate quality records. Exposures generally lower than for previous group.
24 17 12 2 5 4	Not in 1976 study but open. Tend to be smaller mines, have poorer records, and lower exposures. Two mines (12, 24) were from companies with mines in the high priority category.
11 22 20 9 3 1 14 10	Not in 1976 study. Have a combination of small size, poor records, closed, or very low diesel usage. (Note: the ordering within this group is very approximate.)

Table B.2 Relative ranking of 24 feasibility mines into priority order of importance to the study. Mines will be included in the study in this order. (Note that the ordering is somewhat approximate, and logistical issues may dictate final order in which mines are surveyed.)

A few explanatory notes are necessary concerning Table B.2. Mine 20, though very large and having good records, was found to have minimal diesel equipment usage. Since its extreme size meant it would have dominated the mortality analysis, and because of its very low exposures, its inclusion was felt to be unwarranted, and it was relegated to the low priority group. Most of the records for mine 2 were stored offsite and were not available during the feasibility survey. Accordingly, its estimated number of lung cancer deaths is probably grossly underestimated.

On the basis of the information in Table B.1 it was found that the ten mines in the top half of Table B.2 are expected to supply sufficient cases for the case-control study, given that half the workforce was

exposed to diesel exhaust, and given a OR of about 1.7 for the exposed group. This cohort would comprise about 8,200 miners contributing 184,000 person-years to the analysis.

The plan for the study is to survey the mines in priority order as shown in Table B.2. Data entry and mortality follow-up will be proceeding concurrently with data collection. Therefore, while the study is progressing it will be possible to assess the likely number of lung cancer cases that will occur in those mines already surveyed based on the expected person-years and assumed risk of lung cancer. When it appears that the target of 160 will be exceeded, we will cease surveying further mines. Hence, through use of this approach, and given that we have likely and unavoidably underestimated the mine employment at some mines, it may be possible to include fewer than 10 mines in the study. In this way, the study will be made as expeditious as possible. Alternatively, unforeseen circumstances may require that we have to include some additional mines. (Note that while we expect to hold to the priority order, logistical considerations will play some role in the sequence in which mines are visited.)

APPENDIX C - INFORMATION ON RADON AND SILICA LEVELS

Information from the MIDAS database on radon and silica levels for the 24 feasibility mines selected for study for the years 1973 to date is shown in Table C.1. The radon values are from area samples, while the silica data are from personal samples. All data are MSHA compliance data.

MINE ID NUMBER	RADON		RESPIRABLE SILICA		
	N	Mean Conc. (WL)	N	Mean % of total dust	Mean Conc. ($\mu g/m^3$)
1	9	0.010	37	0.4	3.2
2	10	0.008	37	0.4	1.5
3	14	0.002	59	2.2	19.9
4	21	0.002	42	0.1	0
5	12	0.010	28	0.6	6.8
6	36	0.002	99	0.5	16.1
7	13	0.005	53	0.2	24.9
8	50	0.006	111	0.3	12.6
9	9	0.012	73	0.2	2.6
10	76	0.013	93	0	0
11	83	0.038	42	1.1	13.9
12	36	0.012	11	1.1	6.2
13	35	0.015	4	0.0	0.0
14	32	0.005	97	0.8	3.7
15	33	0.015	120	0.2	1.5
16	18	0.009	28	3.0	13.4
17	20	0.009	10	0.5	1.2
18	13	0.005	16	1.6	16.3
19	10	0.003	21	0.2	9.8
20	24	0.008	21	0.1	0.1
21	21	0.015	10	0.4	2.9
22	18	0.000	34	0.5	3.9
23	31	0.000	73	0.2	5.3
24	23	0.008	81	0.3	1.6

Table C.1 Information from the MIDAS database on radon and silica for the selected primary and back-up mines

APPENDIX D - PRECISION OF ELEMENTAL CARBON METHOD

D.1 Introduction

Diesel exhaust is a complex mixture of noxious gases such as carbon monoxide (CO) , carbon dioxide (CO_2), nitric oxide (NO), nitrogen dioxide (NO_2), and sulfur dioxide (SO_2), hundreds of different hydrocarbons (HCs), and diesel particulate matter (DPM). DPM, itself, is a complex mixture of chemical compounds. It is composed of nonvolatile, elemental carbon (EC), hundreds of different adsorbed or condensed HCs, sulfates, and trace quantities of metallic compounds. DPM is of special concern because it is entirely respirable in size, with 90% of the particles, by mass, having an equivalent aerodynamic diameter of less than 1.0 μm. This means that the particles can penetrate to the deepest regions of the lungs and, if retained, may cause or contribute to the development of lung disease.[104]

Currently, elemental carbon is considered to be the best surrogate measure of diesel particulate matter in the occupational environment.[104] In general, EC accounts for about 40 - 60% of the mass of DPM, but this percentage varies depending upon engine duty cycle, fuel quality, after-treatment device and other factors.[104] The analytical method refined and adopted by NIOSH as Method 5040 was originally developed for separating organic from elemental carbon aerosols in the atmosphere. This technique is a sensitive measure of the elemental carbon portion of diesel exhaust aerosol. and can detect as little as 1 $\mu g/m^3$ of EC. EC is generally a specific marker of diesel exhaust, even when other combustion aerosols (e.g., wood smoke, cigarette smoke) are present, because many of these aerosols contain negligible or relatively small amounts of EC.

D.2 precision of side-by-side elemental carbon measurements

Several groups of investigators have conducted side-by-side studies of elemental carbon precision in-mine. In 33 sets of samples conducted over a several years, NIOSH samples ranged from 0.003 - 1.04 mg/m^3. Correlation analysis of the side-by-side samples showed excellent agreement ($r = 0.95$). The standard deviation of the sample difference was 0.013 and $t = 0.55$ ($p>0.5$). This resulted in a p-value of greater than 0.5, which indicates that the two sample sets are not different.

To evaluate the precision of the EC sampling method, MSHA collected elemental carbon samples using a sample chamber with 30 sampling ports. The chamber was typically set up to hold either 5 or 10 elemental carbon samplers. Results from 11 different studies conducted in this way permit us to evaluate the precision of the EC sampling method further. Table I lists some of their results.

Study	Number of Samples	AVG	STD	COV (%)
1	10	0.150	0.010	4.1
2	10	0.450	0.050	10.2
3	10	0.420	0.040	10.0
4	5	0.178	0.006	3.6
5	4	0.341	0.016	4.8
6	5	0.108	0.014	13.2
7	5	0.053	0.017	11.0
8	5	0.054	0.002	3.5
9	4	0.045	0.002	4.8
10	5	0.018	0.003	14.9
11	5	0.030	0.003	11.2

TABLE D.1 Side-by-side Elemental Carbon Samples of MSHA data from 11 studies

As is demonstrated in the table above, the coefficients of variation (COV) ranged from 3.5% to 14.9%. The mean COV over the 11 studies was 8.3%, which shows that the precision of the sampling method is good. For example, the precision of the determination of silica in coal dust is 13 - 22% (NIOSH method #7603).[113] The figure of 8.3% compares well with the COV of 7.3% obtained in a study of the trucking industry.[69]

D.3 Elemental carbon NIOSH method 5040

NIOSH has tested and approved Elemental Carbon Method #5040 for publication in the NIOSH Method of Analytical Methods (published in the 1st supplement to the 4th edition). Additionally, NIOSH is sponsoring a round-robin test of a set of standard samples for comparison of results between not only laboratories using the thermo-optical method, but other methods of analyzing elemental carbon as well.

The results to date indicate the following. Total carbon results for nine different laboratories, some of which used an alternative method, were in excellent agreement. The RSDs of the grand means (nine labs) for seven different materials ranged from 7-13%. In contrast to results obtained by the alternative method (based on coulometric determination of CO_2), which quantified about 70% of the carbon in an organic standard as elemental, the thermal-optical method effectively discriminated against char form during the analysis. Less than 0.2 % of the carbon found in this sample was measured as EC. In general, EC results obtained by the thermal-optical method were lower than those obtained by the alternative approach, which gave a less specific measure of EC and OC. Preliminary results of thermal-optical analysis of two samples of diesel particulate (diesel fire engine and truck) indicate an interlaboratory precision (five laboratories) of about 20%. This value includes the variability in loading across the 8" x

10" quartz-fiber filter (about 3% based on measurement of total carbon). The across-filter variability in the mean EC (found by multiple analyses of the filters) was about 8%. The samples analyzed were complex in that OC evolved over a wide temperature range and some pyrolysis was apparent. Because of their complexity, results for these samples represent a likely worst-case scenario with respect to the between-laboratory precision of the analysis. Results of the round-robin will be presented at an international conference on elemental speciation, which will be held in Australia, September 15-20, 1997.[114] Proceedings of the conference will be published (likely in late '97) in a special issue of the journal Analyst. (E. Birch, Personal communication, 1996).

APPENDIX E - IH INFORMATION FROM THE FEASIBILITY STUDY MINE

This following information is a tabulation of information summarized from samples collected during the feasibility study at mine 16. It includes mean exposure levels of CO_2, CO, NO, NO_2, SO_2, total dust, respirable dust, submicrometer dust, and elemental carbon for various zones of the mine using area samples. This appendix was prepared by Ms. Patricia Brower, a statistician in the Epidemiological Investigations Branch of the Division of Respiratory Disease Studies at NIOSH..

Table E.1 Mean Concentration for CO_2 (ppm), CO (ppm), NO (ppm), NO_2 (ppm), SO_2 (ppm), Total Dust (mg/m^3), Respirable Dust (mg/m^3), Submicrometer Dust (mg/m^3), and Elemental Carbon (mg/m^3) by Area.

Area	Contaminant	N	Mean	Min, Max
Auto Shop				
	CO_2 (ppm)	2	702.04	663.9, 740.1
	CO (ppm)	3	1.82	1.32, 2.66
	NO (ppm)	6	0.03	0.001, 0.07
	NO_2 (ppm)	6	0.02	0.003, 0.04
	SO_2 (ppm)	3	0.46	0.18, 0.66
	Total Dust (mg/m^3)	5	0.14	0.06, 0.26
	Respirable Dust (mg/m^3)	4	0.19	0.08, 0.45
	Submicrometer Dust (mg/m^3)	4	0.18	0.12, 0.28
	Elemental Carbon (mg/m^3)	6	0.02	0.003, 0.08
Haulage				
	CO_2 (ppm)	2	1441.38	1041.7, 1841.1
	CO (ppm)	5	7.26	6.11, 8.33
	NO (ppm)	8*	3.31	0.05, 5.38
	NO_2 (ppm)	9	0.91	0.58, 1.55
	SO_2 (ppm)	1	0.48	0.48, 0.48
	Total Dust (mg/m^3)	6	9.36	2.67, 18.28
	Respirable Dust (mg/m^3)	6	2.38	0.99, 3.87
	Submicrometer Dust (mg/m^3)	6	0.76	0.42, 1.23
	Elemental Carbon (mg/m^3)	8	0.14	0.01, 0.34

* Sample values = 0.00 were removed from the analysis (N=1).

Table E.1 (Cont). Mean Concentration for CO_2 (ppm), CO (ppm), NO (ppm), NO_2 (ppm), SO_2 (ppm), Total Dust (mg/m^3), Respirable Dust (mg/m^3), Submicrometer Dust (mg/m^3), and Elemental Carbon (mg/m^3) by Area.

Area	Contaminant	N	Mean	Min, Max
Office				
	CO_2 (ppm)	3	690.76	422.3, 878.4
	CO (ppm)	4	1.74	1.54, 2.20
	NO (ppm)	3	0.004	0.00, 0.01
	NO_2 (ppm)	3	0.00	0.00, 0.00
	SO_2 (ppm)	1	0.93	0.93, 0.93
	Total Dust (mg/m^3)	4	0.19	0.00, 0.62
	Respirable Dust (mg/m^3)	4	0.16	0.06, 0.26
	Submicrometer Dust (mg/m^3)	4	0.18	0.12, 0.22
	Elemental Carbon (mg/m^3)	4	0.002	0.0001, 0.005
Diesel Shop				
	CO_2 (ppm)	4	680.39	570.6, 800.1
	CO (ppm)	4	1.95	0.82, 2.53
	NO (ppm)	8*	0.16	0.01, 0.26
	NO_2 (ppm)	9	0.06	0.01, 0.09
	SO_2 (ppm)	2	0.79	0.63, 0.95
	Total Dust (mg/m^3)	5	1.04	0.03, 3.37
	Respirable Dust (mg/m^3)	6	0.80	0.00, 3.42
	Submicrometer Dust (mg/m^3)	7	0.31	0.10, 0.53
	Elemental Carbon (mg/m^3)	8	0.04	0.004, 0.07

* Sample values = 0.00 were removed from the analysis (N=1).

Table E.1 (Cont). Mean Concentration for CO_2 (ppm), CO (ppm), NO (ppm), NO_2 (ppm), SO_2 (ppm), Total Dust (mg/m^3), Respirable Dust (mg/m^3), Submicrometer Dust (mg/m^3), and Elemental Carbon (mg/m^3) by Area.

Area	Contaminant	N	Mean	Min, Max
Ram Car				
	CO_2 (ppm)	3	1477.89	1308.7, 1750.0
	CO (ppm)	5	5.51	4.96, 6.86
	NO (ppm)	9	2.42	0.00, 4.56
	NO_2 (ppm)	9	0.86	0.45, 1.59
	SO_2 (ppm)	2	0.57	0.38, 0.76
	Total Dust (mg/m^3)	7	4.30	0.47, 17.18
	Respirable Dust (mg/m^3)	7	0.87	0.19, 2.16
	Submicrometer Dust (mg/m^3)	7	0.80	0.59, 1.04
	Elemental Carbon (mg/m^3)	6	0.27	0.16, 0.36
Top Side				
	CO_2 (ppm)	4	541.62	295.1, 657.9
	CO (ppm)	4	2.04	0.87, 3.29
	NO (ppm)	6	0.18	0.08, 0.34
	NO_2 (ppm)	6	0.04	0.01, 0.07
	SO_2 (ppm)	0	--	--
	Total Dust (mg/m^3)	5	0.25	0.11, 0.40
	Respirable Dust (mg/m^3)	4	0.12	0.05, 0.29
	Submicrometer Dust (mg/m^3)	4	0.23	0.14, 0.28
	Elemental Carbon (mg/m^3)	6	0.01	0.01, 0.02

Table E.2 Correlation between CO_2, CO, NO, NO_2, SO_2, Total Dust, Respirable Dust, Submicrometer Dust, and Elemental Carbon based on individual samples.

Contaminant	Contaminant								
	CO_2	CO	NO	NO_2	SO_2	Total Dust	Resp. Dust	Sub. Dust	Elemental Carbon
CO_2	1.00	--	--	--	--	--	--	--	--
CO	0.90	1.00	--	--	--	--	--	--	--
NO	0.75	0.80	1.00	--	--	--	--	--	--
NO_2	0.69	0.80	0.33	1.00	--	--	--	--	--
SO_2	-0.09	-0.19	-0.09	-0.13	1.00	--	--	--	--
Total Dust	0.68	0.62	0.78	0.31	-0.49	1.00	--	--	--
Resp. Dust	0.79	0.71	0.82	0.30	-0.53	0.77	1.00	--	--
Sub. Dust	0.91	0.77	0.83	0.53	-0.50	0.73	0.61	1.00	--
Elemental Carbon	0.59	0.53	0.48	0.64	0.19	0.40	0.41	0.71	1.00

Table E.3 Correlation Between the Average CO_2, CO, NO, NO_2, SO_2, Total Dust, Respirable Dust, Submicrometer Dust, and Elemental Carbon (Averaged Within Six Areas).

Average Contaminant	Average Contaminant								
	CO_2	CO	NO	NO_2	SO_2	Total Dust	Resp. Dust	Sub. Dust	Elemental Carbon
CO_2	1.00	--	--	--	--	--	--	--	--
CO	0.95	1.00	--	--	--	--	--	--	--
NO	0.96	0.99	1.00	--	--	--	--	--	--
NO_2	0.98	0.98	0.99	1.00	--	--	--	--	--
SO_2	-0.54	-0.56	-0.55	-0.54	1.00	--	--	--	--
Total Dust	0.88	0.97	0.96	0.91	-0.52	1.00	--	--	--
Resp. Dust	0.77	0.89	0.88	0.81	-0.44	0.96	1.00	--	--
Sub. Dust	0.97	0.95	0.96	0.99	-0.48	0.88	0.79	1.00	--
Elemental Carbon	0.92	0.80	0.82	0.90	-0.44	0.66	0.52	0.93	1.00

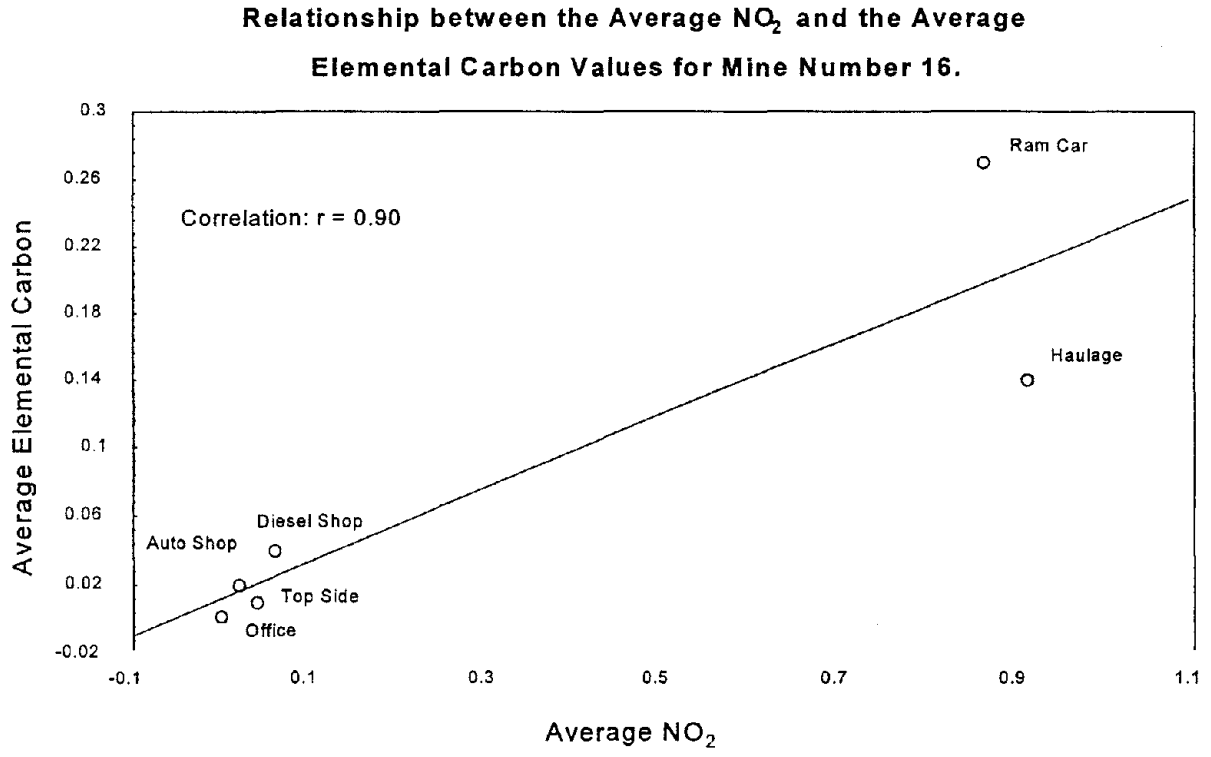

Figure E.1 Relationship between NO_2 and elemental carbon

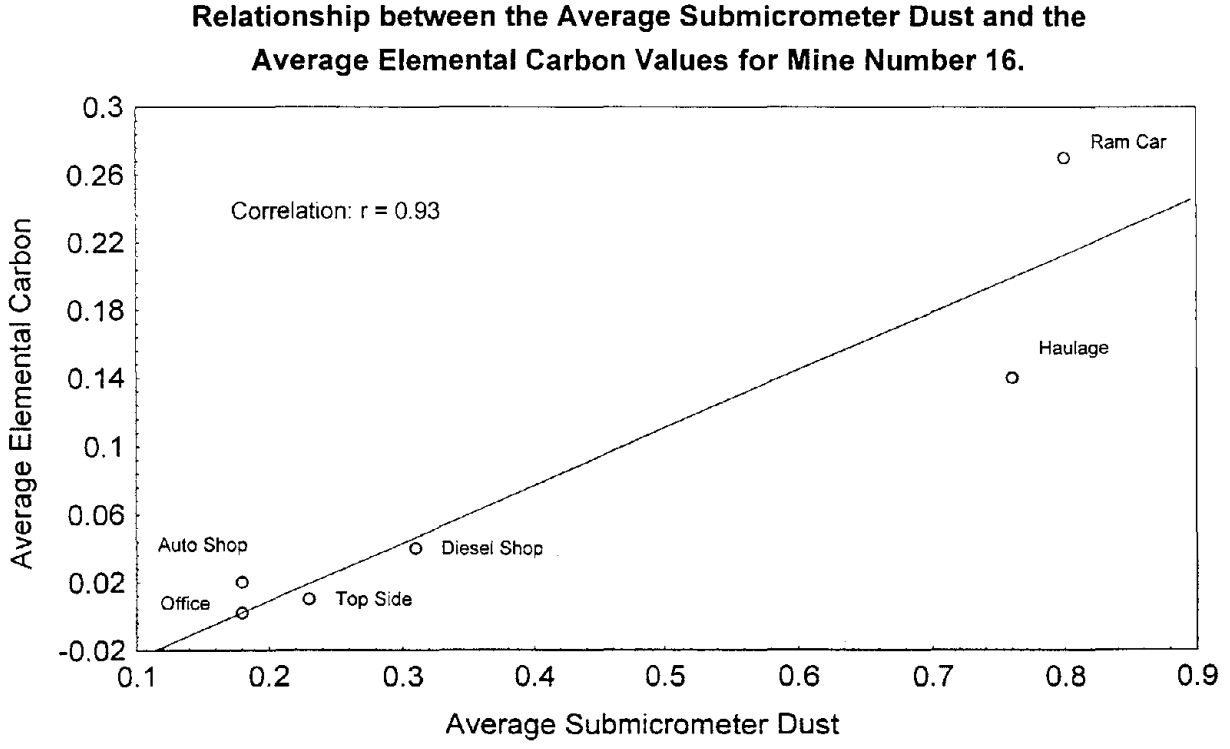

Figure E.2 Relationship between submicrometer dust and elemental carbon

Relationship between the Average Submicrometer Dust and the Average NO_2 Values for Mine Number 16.

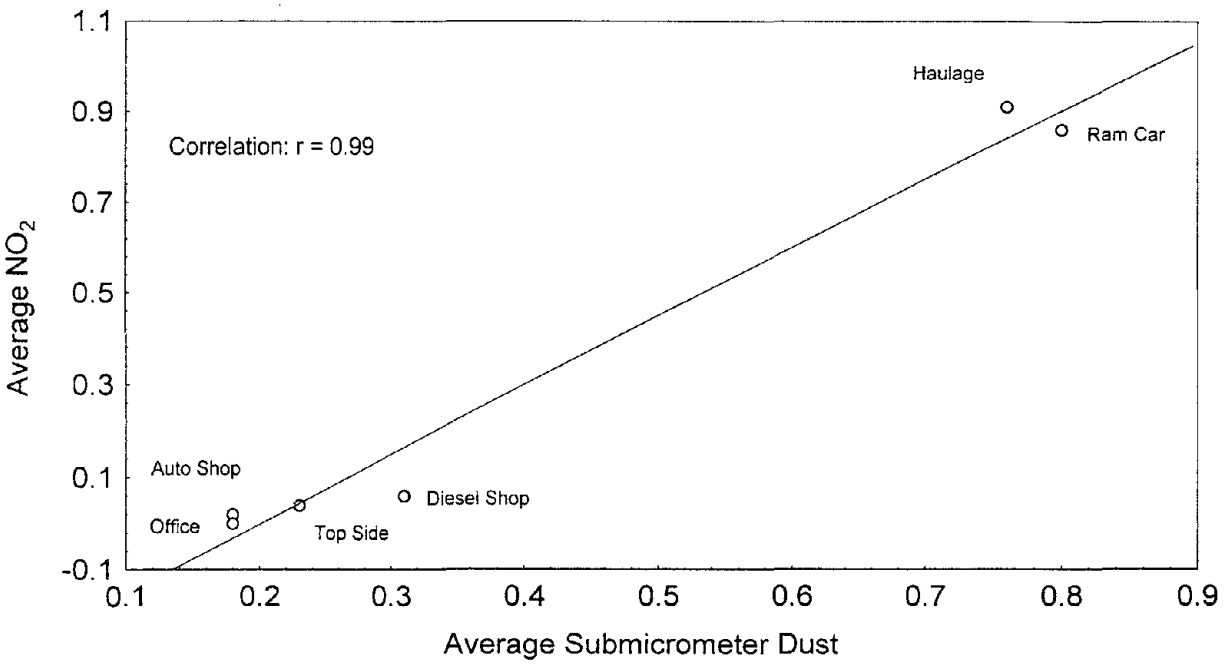

Figure E.3 Relationship between submicrometer dust and NO_2

APPENDIX F. ANALYSIS OF THE PERSONAL AND AREA SAMPLES FROM THE 1976-78 MSHA ENVIRONMENTAL SURVEY FOR SEVEN NON-METAL MINES.

F.1 Introduction

A univariate analysis was performed on the environmental samples that were collected by MSHA during a 1976-78 survey. There were a total of 21 metal and non-metal mines which participated in the NIOSH/MSHA morbidity study. Of these, seven were chosen for the inclusion in the mortality study.

F.2 Objective

To tabulate the mean level and variability of the measurements taken during the 1976-78 environmental survey. For each of the seven non-metal mines, the overall variability, and the between and within job title variabilities was also determined.

F.3 Outline

The first part of this report analyzes the personal sample measurements of total dust, NO_2, and percent quartz for each of the seven mines. A natural logarithmic transformation was used when it was deemed necessary. Box and whisker plots were created by job title for each environmental sample. The job titles were obtained from two sources: 1) Personnel files and 2) Sampler at the time of sampling.

The second part of this report analyzes the area sample measurements for each of the seven mines. Gravimetric samples were taken for total dust and respirable dust. Total hydrocarbons (HC) were measured from charcoal tube detectors. Bistable and vacuum bottle samplers measured percent oxygen (O_2), carbon monoxide (CO), percent carbon dioxide (CO_2), methane (CH_4), and total hydrocarbons (HC). A natural logarithmic transformation was applied when necessary. Frequency plots were created by location for each environmental sample.

F.4 Results

F.4.1 Personal Samples

Table F.1 presents the geometric mean, geometric standard deviation, and the geometric quartiles (25th, 50th, and 75th) for each environmental sample by mine. For mine number 21, the arithmetic values were given for NO_2. For mine number 8, the arithmetic values were given for percent quartz. The natural logarithmic transformation was not useful in normalizing these distributions.

For mine numbers 13, 16, 18, 19, and 21 non-detectable values were recorded for percent quartz. Table F.2 shows the percentage of non-detectable values (censored observations) and the geometric standard deviation of the non-censored observations for each of these mines. Hornung and Reed[f] have summarized four methods used in estimating the average concentration when non-detectable values exist. These methods are Cohen's Method, Hald's Method, LOD/2 method, and LOD/$\sqrt{2}$ Method. Hornung and Reed suggest that the best approach is either Cohen's or Hald's method. However, these two

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[f] Hornung R.W. and L. D. Reed: Estimation of Average Concentration in the Presence of Nondetectable Values. *Appl. Occup. Environ. Hyg.* 5(1): 1990.

methods required a considerable amount of calculation and the require many tables. Of the other two approaches, if the geometric standard deviation of the non-censored values approach 3.0 and the percentage of censored observations approach 100% then the LOD/2 is the best for estimating the geometric mean and geometric standard deviation as compared to the LOD/$\sqrt{2}$ method. With the help of tables provided by Hornung and Reed, the LOD/2 method was chosen for the non-detectable values recorded for mine numbers 13, 16, 18, 19, and 21. For mine numbers 6, 18, and 19, some zero values were recorded for NO_2. These values were treated as non-detectable measurements, and the LOD/2 method was applied to them also. For mine number 19, the LOD/$\sqrt{2}$ method was also employed; however, there was no difference between the two methods in the estimated geometric mean and geometric standard deviation.

Table F.3 shows the percent frequency distribution of job title for each mine. For mine numbers 18 and 19, two job titles were given. The first job title was from the personnel files, and the second job title was reported by the sampler at the time of sampling. The value in the parenthesis corresponds to the job title reported by the sampler.

For each mine, box and whisker plots (Figure F.1 - Figure F.27) were created for each environmental sample by job title. For mine numbers 18 and 19, two sets of plots were created, one set representing the job titles from the personnel files and the other set representing the job titles recorded by the sampler at the time of sampling. The top and bottom of the box represents the 25th and 75th percentiles. The line in the box represents the median value. The whiskers of the box represent the minimum and maximum values.

F.4.2 Area Samples

The following results are for gravimetric area samples. The analyses for charcoal tube detectors, bistable and vacuum bottle samplers have not yet been completed.

Table F.4 presents the average, standard deviation, and quartiles for each gravimetric, environmental area sample by mine. For mine numbers 6 and 16, both total and respirable dust values were $\log_e$ transformed and geometric averages, standard deviations, and quartiles were calculated. For mine numbers 13, 19, and 21, geometric values were given only for total dust.

Table F.5 shows the percentage of values that fall within two, or three standard errors of the overall average value of total and respirable dust by mine. For example, of the 20 total dust samples taken within mine number 13, 42% of them were within two standard errors of the overall average total dust of the mine, and 45% were within three standard errors.

Acknowledgment

Descriptive analysis and report writing were prepared by Ms. Patricia Brower, a statistician in the Epidemiological Investigations Branch of the Division of Respiratory Disease Studies at NIOSH.

Table F.1 Overall Analysis for Total Dust, NO_2, and Percent Quartz.

Mine Number		N	GM	GSD	Quartiles (25th, 50th, 75th)
6	Total Dust	94	10.6	2.9	4.5, 11.3, 27.6
	NO_2*	93	0.1	2.6	0.04, 0.1, 0.2
	Percent Quartz	93	1.5	1.8	1.0, 1.5, 2.1
8	Total Dust	85	7.8	2.8	5.1, 8.5, 13.4
	NO_2	85	0.1	1.9	0.06, 0.10, 0.14
	Percent Quartz**	85	1.3	0.5	1.0, 1.2, 1.5
13	Total Dust	99	2.7	3.8	1.1, 3.2, 5.7
	NO_2	100	0.7	1.9	0.5, 0.7, 1.0
	Percent Quartz*	99	0.1	5.9	0.04, 0.1, 0.3
16	Total Dust	96	2.9	3.4	1.4, 2.5, 5.8
	NO_2	96	0.2	2.3	0.1, 0.2, 0.3
	Percent Quartz*	97	0.1	4.6	0.05, 0.05, 0.5
18	Total Dust	103	8.9	2.8	4.7, 9.4, 18.1
	NO_2*	94	0.5	3.8	0.3, 0.6, 1.4
	Percent Quartz*	103	0.3	3.4	0.1, 0.3, 0.6
19	Total Dust	81	6.2	2.7	3.1, 6.6, 11.7
	NO_2*	80	0.1	3.1	0.1, 0.2, 0.3
	Percent Quartz*	81	0.1	2.8	0.05, 0.05, 0.2
21	Total Dust	110	5.6	3.1	2.4, 5.0, 13.3
	NO_2**	109	3.2	1.5	2.4, 3.1, 4.2
	Percent Quartz*	107	0.3	3.4	0.1, 0.3, 0.7

* Includes LOD/2. ** Arithmetic values used.

Table F.2 Percent Distribution of Non-Detectable Values Reported for percent quartz[†] and NO_2[*] and the Geometric Standard Deviation of the Non-censored Observations.

Mine Number	Percent Non-Detectable	GSD
13[†]	18	3.2
16[†]	71	2.8
18[†]	24	2.4
19[†]	53	2.4
21[†]	43	2.5
6[*]	1	2.6
18[*]	2	3.2
19[*]	9	2.2

Table F.3 Percent Frequency Distribution of Job Titles by Mine Number.

Mine Number	Job Title								
	Conv. Belt Operator	Electrician	Mechanic	Shot Firer	Miner	Timberme n	Hoisting Service	Cage Tender	Skip Tender
6	--	--	12	3	--	--	--	--	--
8	--	1	29	3	--	--	--	--	--
13	--	5	16	3	3	--	--	1	1
16	7	5	36	1	--	--	--	--	--
18*	--	6 (7)	33 (33)	7 (6)	--	1 (--)	--	2 (1)	--
19*	--	11 (11)	18 (18)	6 (6)	--	--	--	5 (6)	--
21	--	3	33	3	--	--	1	--	--

* Job titles from two sources: personnel files and sampler at time of sampling. The percent inside the () corresponds to job title at time of sampling.

Table F.3 (Cont.). Percent Frequency Distribution of Job Titles by Mine Number.

Mine Number	Job Title							
	Misc. Repairmen	Laborer	Bulldozer Oper.	Continuous Miner	Cutting Mach. Oper.	Joy Loader	Longwall Oper.	Roof Bolter
6	1	22	--	10	3	2	7	12
8	13	1	--	5	3	3	--	10
13	6	18	3	--	3	--	--	3
16	--	10	3	10	1	8	--	1
18*	-- (1)	6 (6)	3 (3)	--	8 (7)	6 (6)	--	1 (1)
19*	--	17 (11)	1 (1)	--	4 (5)	5 (6)	--	4 (6)
21	--	4	1	--	7	5	--	4

* Job titles from two sources: personnel files and sampler at time of sampling. The percent inside the () corresponds to job title at time of sampling.

Table F.3 (Cont.). Percent Frequency Distribution of Job Titles by Mine Number.

Mine Number	Job Title							
	Supervisory & Staff	Shuttle Car Oper.	Payloader	Elec. Hyd. Driller	Construction	Crusher	Truck Driver	Scaler Oper.
6	5	13	2	4	1	--	1	--
8	10	17	--	3	--	--	--	--
13	7	--	8	2	1	2	18	3
16	3	11	1	1	--	--	--	--
18*	9 (9)	11 (12)	--	6 (6)	--	--	--	--
19*	9 (9)	14 (14)	--	6 (6)	--	--	--	--
21	24	10	--	6	--	--	--	--

* Job titles from two sources: personnel files and sampler at time of sampling. The percent inside the () corresponds to job title at time of sampling.

Table F.4 Overall Average Values for Each Gravimetric, Environmental, Area Samples (Total and Respirable Dust) by Mine Number.

Mine Number	Gravimetric Dust Samples	N	Average	Std. Dev.	Quartiles (25th, 50th, 75th)
6	Total	20	3.58*	2.37*	1.96, 3.27, 8.66*
	Respirable	19	1.25*	2.07*	0.81, 1.39, 2.41*
8	Total	20	5.96	3.93	3.38, 5.36, 9.01
	Respirable	20	1.89	1.16	0.93, 1.82, 2.52
13	Total	20	2.18*	5.27*	0.85, 1.95, 9.08*
	Respirable	19	0.73	0.46	0.30, 0.70, 1.10
16	Total	20	1.63*	3.62*	0.63, 1.01, 4.29*
	Respirable	13	0.65*	1.80*	0.49, 0.59, 0.82*
18	Total	18	4.75	2.90	2.95, 4.36, 6.63
	Respirable	18	0.78	0.51	0.29, 0.76, 1.12
19	Total	18	2.93*	1.87*	1.94, 3.19, 4.24*
	Respirable	20	0.83	0.34	0.54, 0.88, 0.97
21	Total	18	2.54*	3.67*	1.17, 2.94, 5.75*
	Respirable	18	1.17	0.68	0.73, 1.19, 1.73

* Geometric mean, standard deviation, and quartiles were used when data were not normally distributed.

Table F.5 Percentage of Values within Two (Three) Standard Errors of the Overall Average Value of Total and Respirable Dust by Mine Number.

Mine Number	N	Total Dust	N	Respirable Dust
6	20	35 (45)	19	42 (53)
8	20	30 (50)	20	45 (45)
13	20	42 (45)	19	37 (47)
16	20	20 (35)	13	62 (69)
18	18	33 (56)	18	28 (44)
19	18	44 (61)	20	40 (55)
21	18	39 (67)	18	28 (39)

Figure F.1. Distribution of Total Dust (exp(ln(total dust))) by Job Title for Mine Number 6

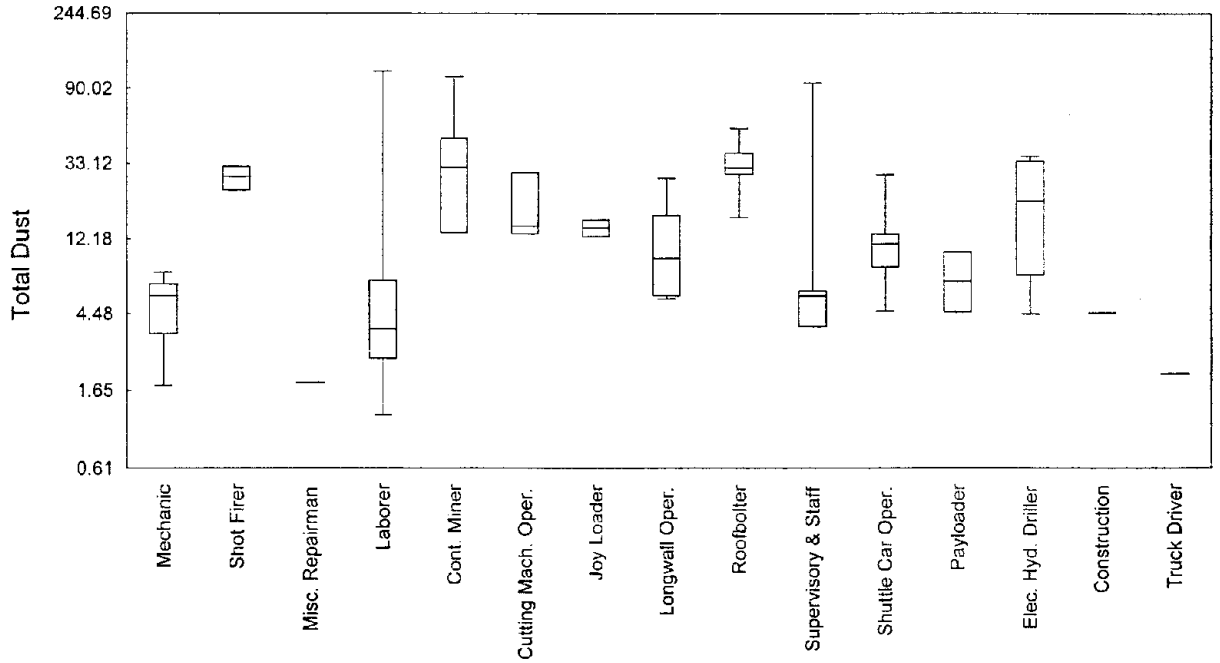


Figure F.2. Distribution of NO_2 (exp(ln(NO_2))) by Job Title for Mine Number 6

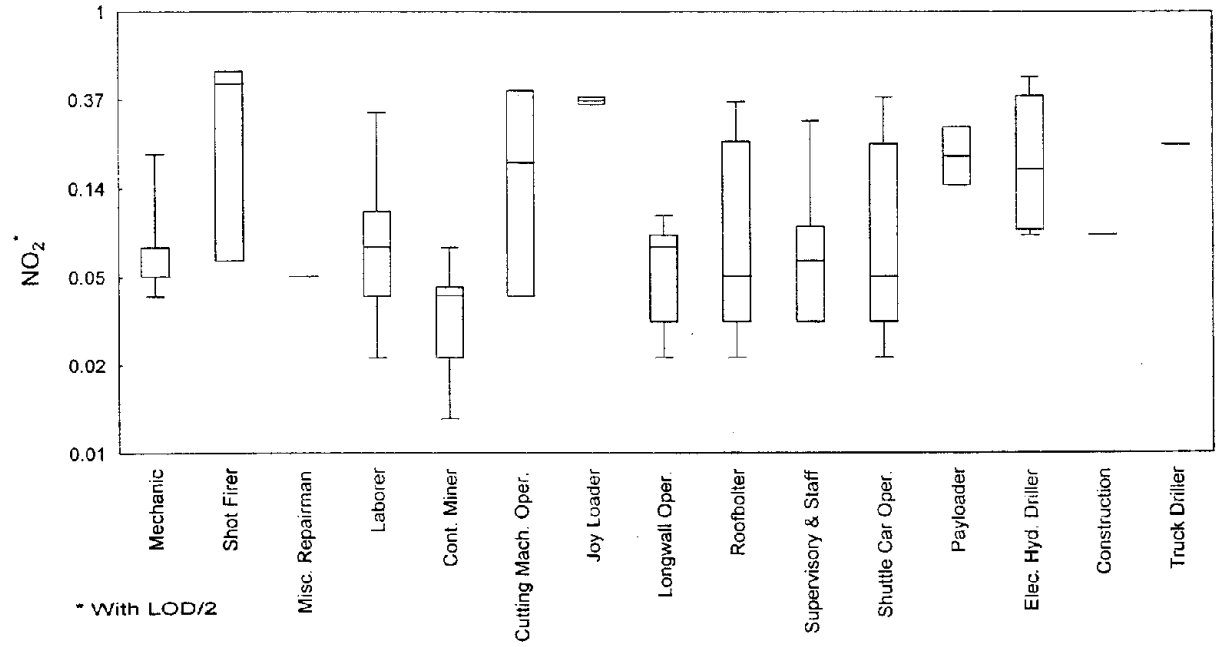


Figure F.3. Distribution of Percent Quartz (exp(ln(%qrtz))) by Job Title for Mine Number 6

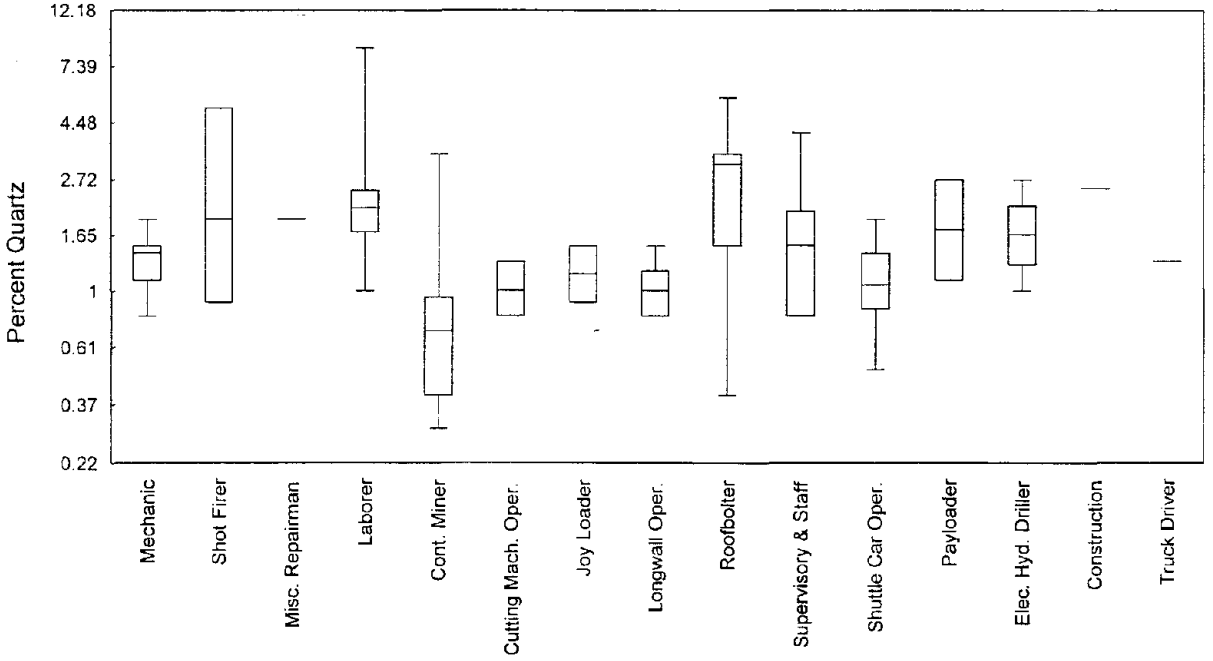


Figure F.4. Distribution of Total Dust (exp(ln(total dust))) by Job Title for Mine Number 8

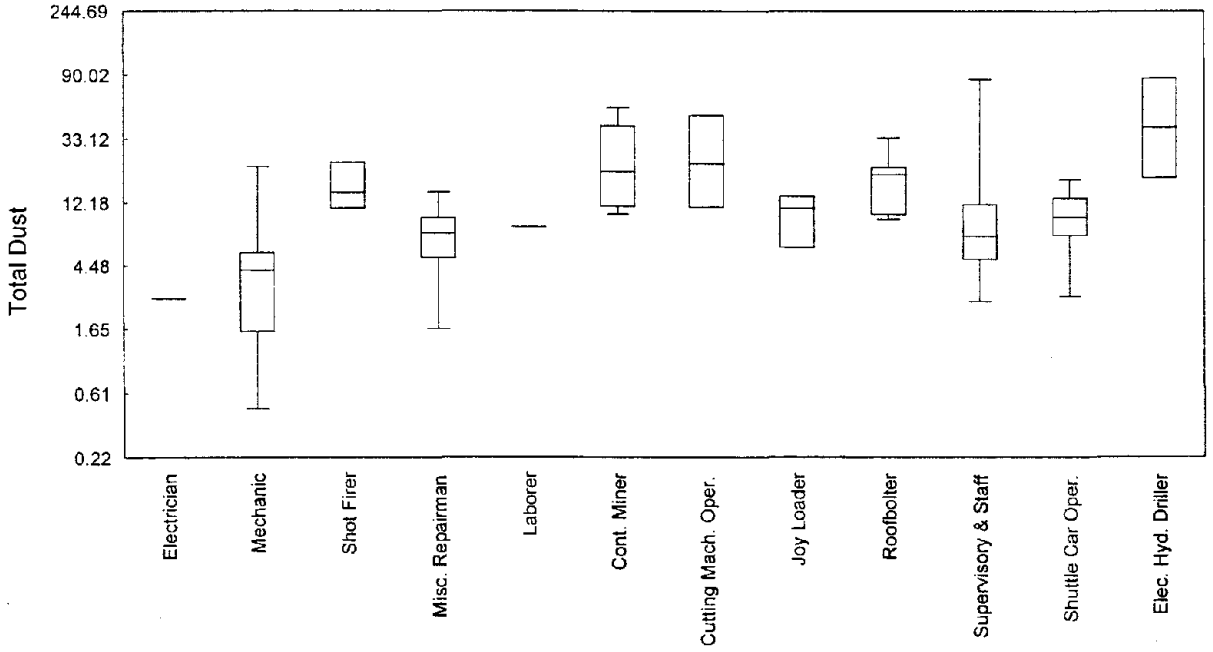


Figure F.5. Distribution of NO_2 (exp(ln(NO_2))) by Job Title for Mine Number 8

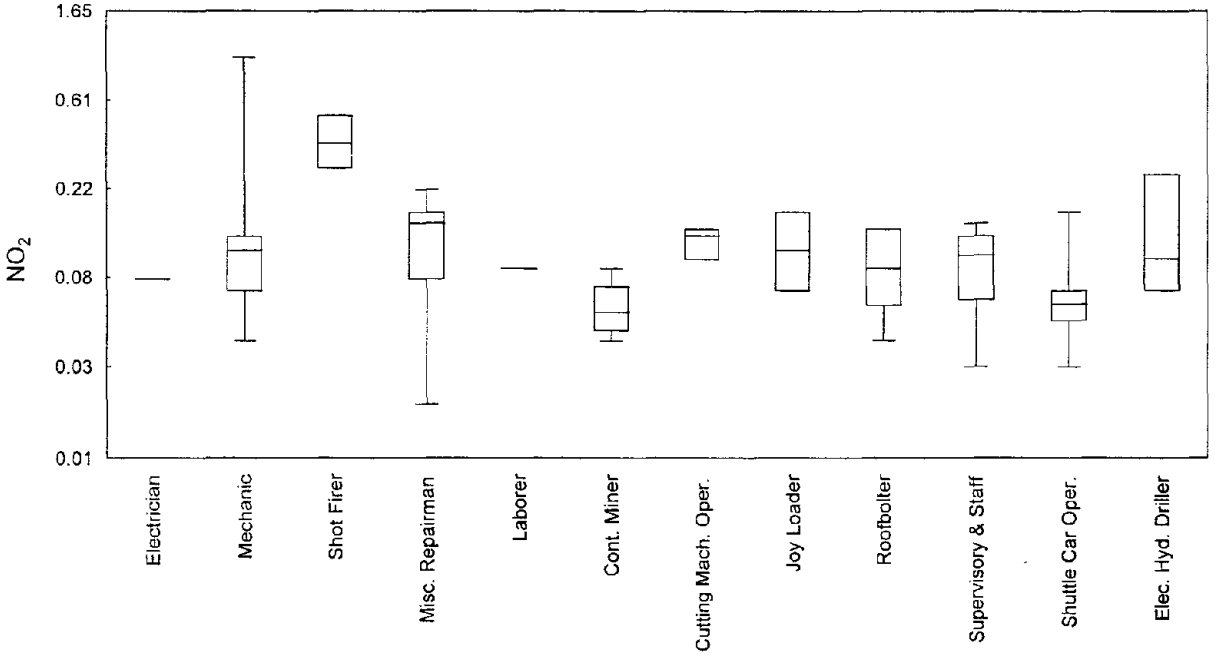


Figure F.6. Distribution of Percent Quartz by Job Title for Mine Number 8

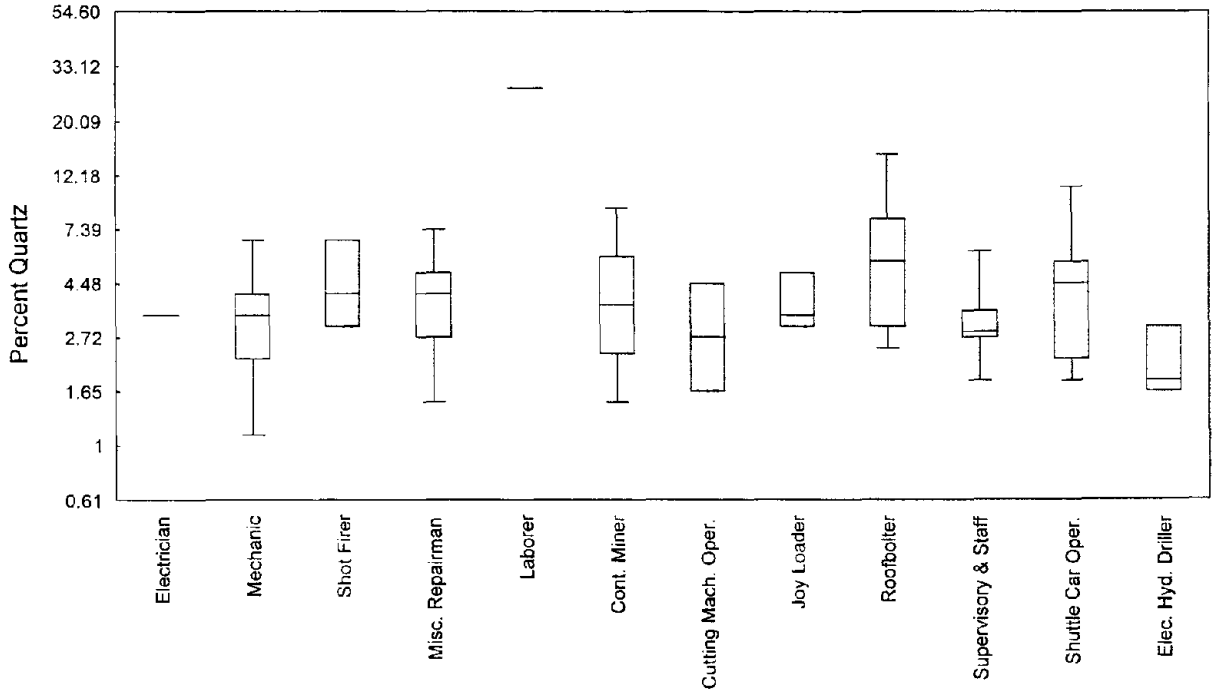


Figure F.7. Distribution of Total Dust (exp(ln(total dust))) by Job Title for Mine Number 13

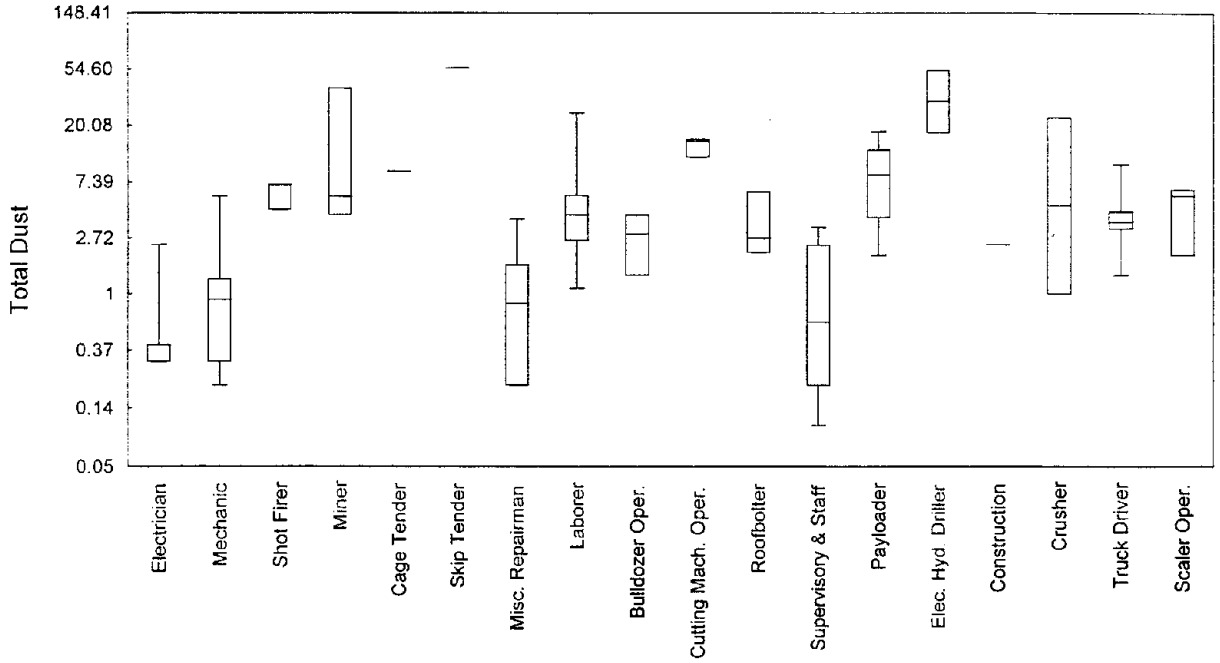


Figure F.8. Distribution of NO_2 (exp(ln(NO_2))) by Job Title for Mine Number 13

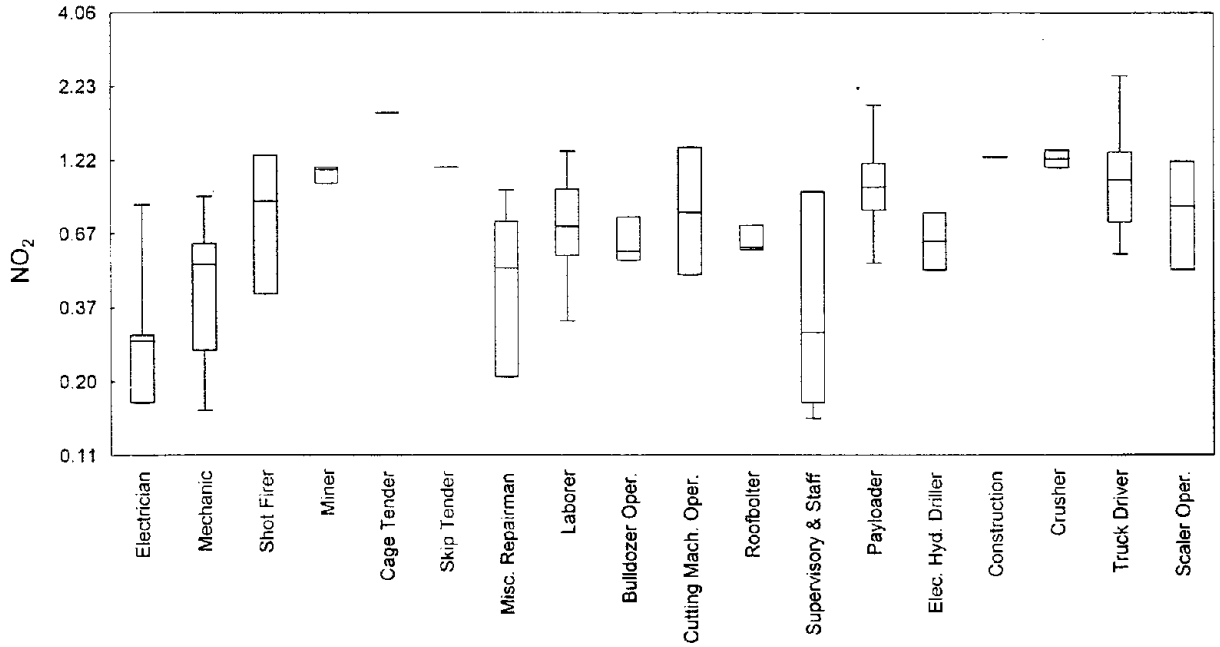


Figure F.9. Distribution of Percent Quartz (exp(ln(%qrtz))) by Job Title for Mine Number 13

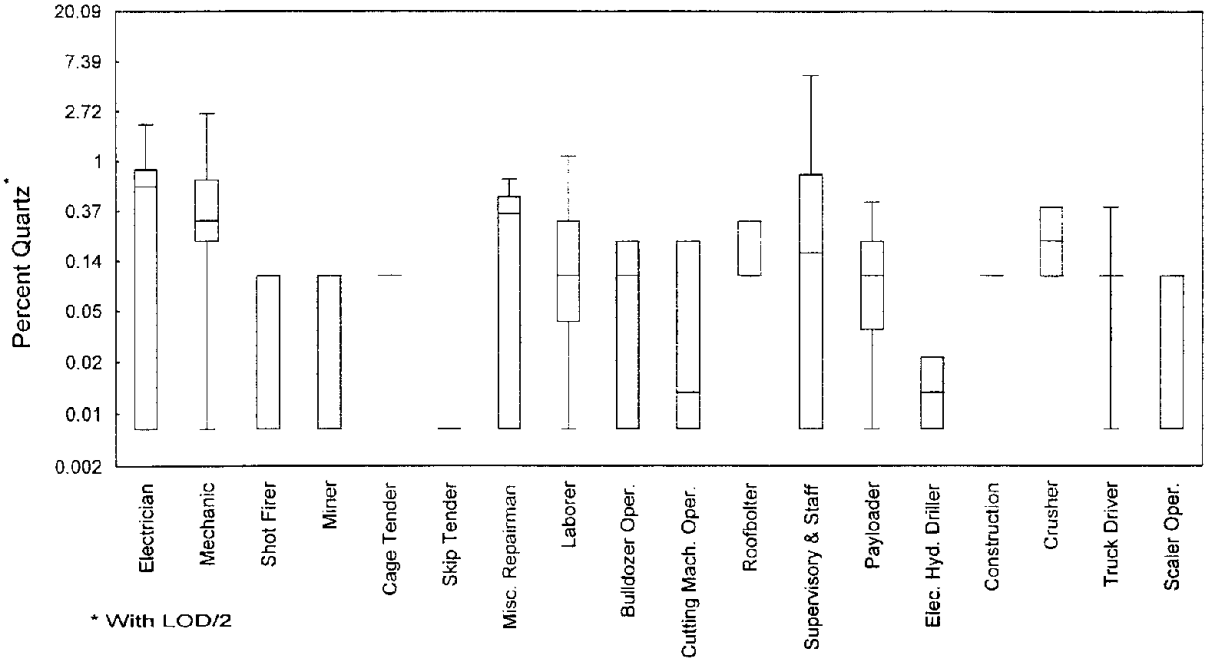


Figure F.10. Distribution of Total Dust (exp(ln(total dust))) by Job Title for Mine Number 16

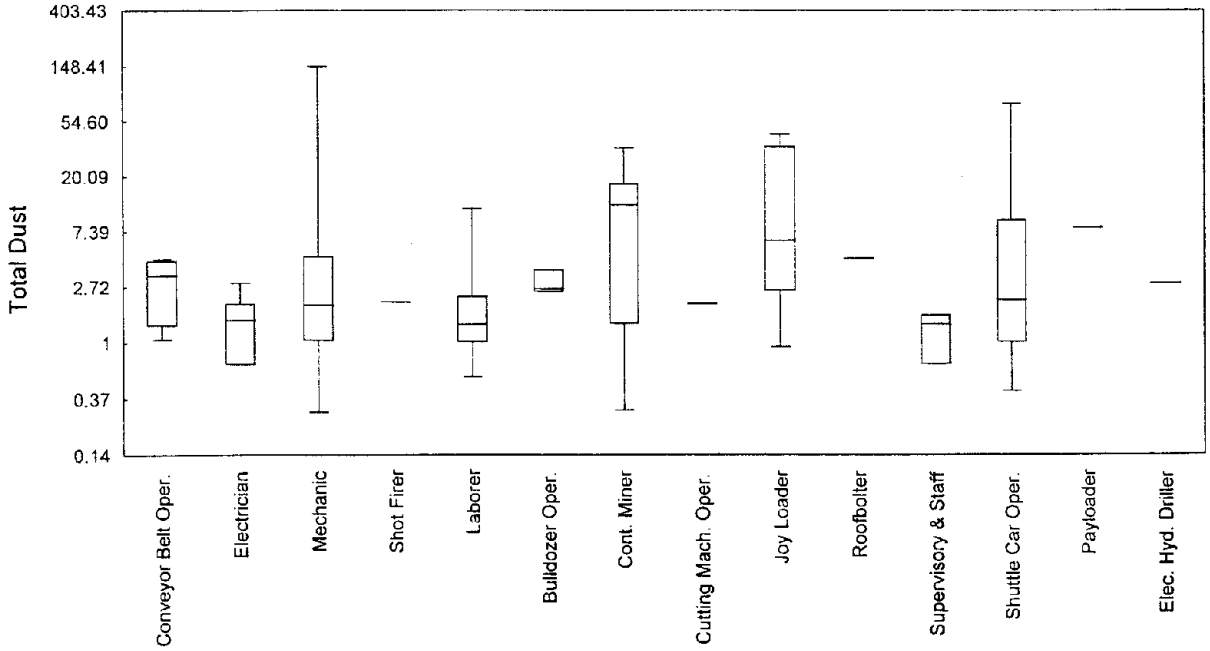


Figure F.11. Distribution of NO_2 (exp(ln(NO_2))) by Job Title for Mine Number 16

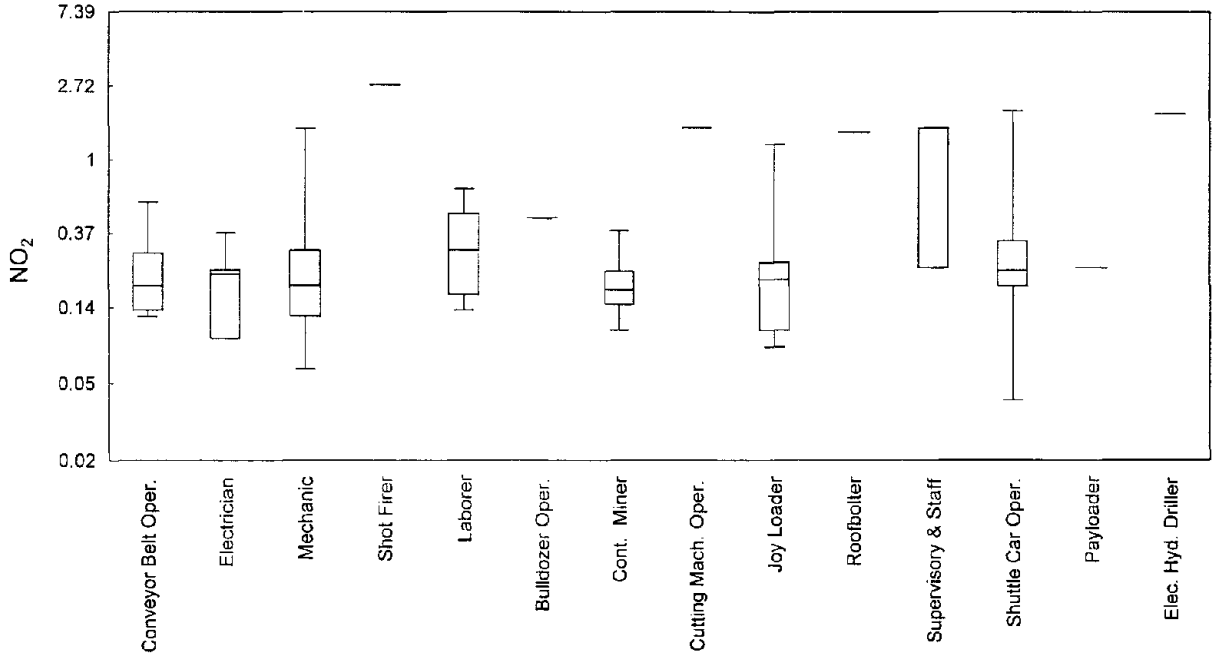


Figure F.12. Distribution of Percent Quartz (exp(ln(%qrtz))) by Job Title for Mine Number 16

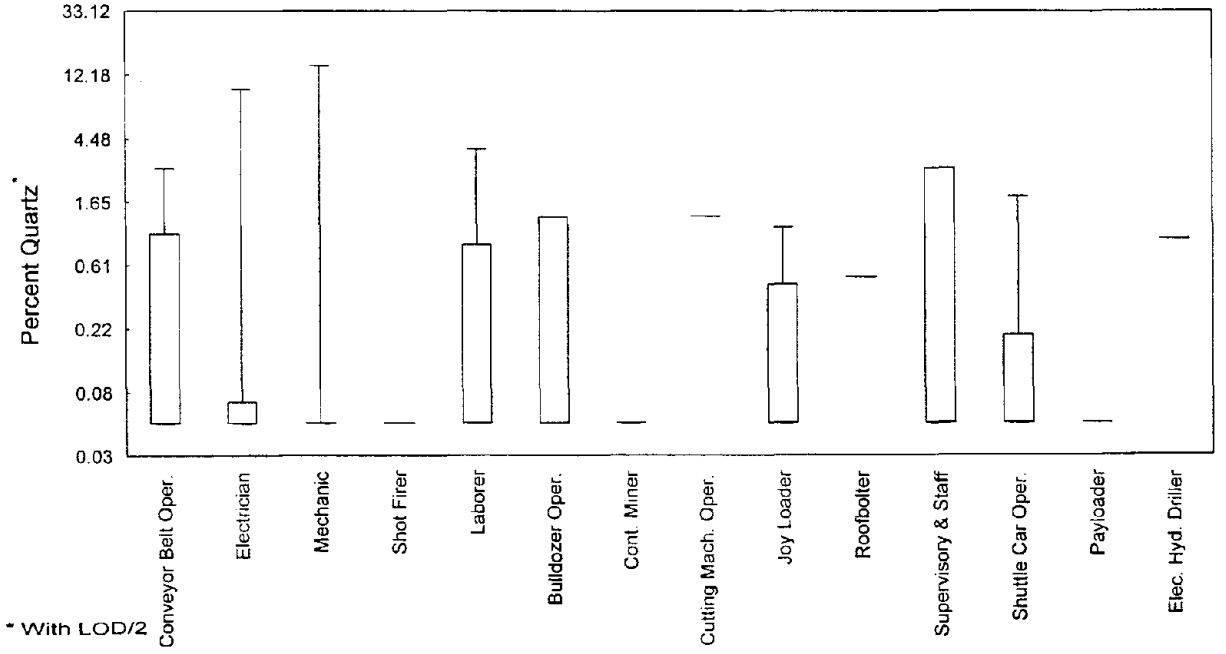


Figure F.13. Distribution of Total Dust (exp(ln(total dust))) by Job Title for Mine Number 18

(Personnel Files)

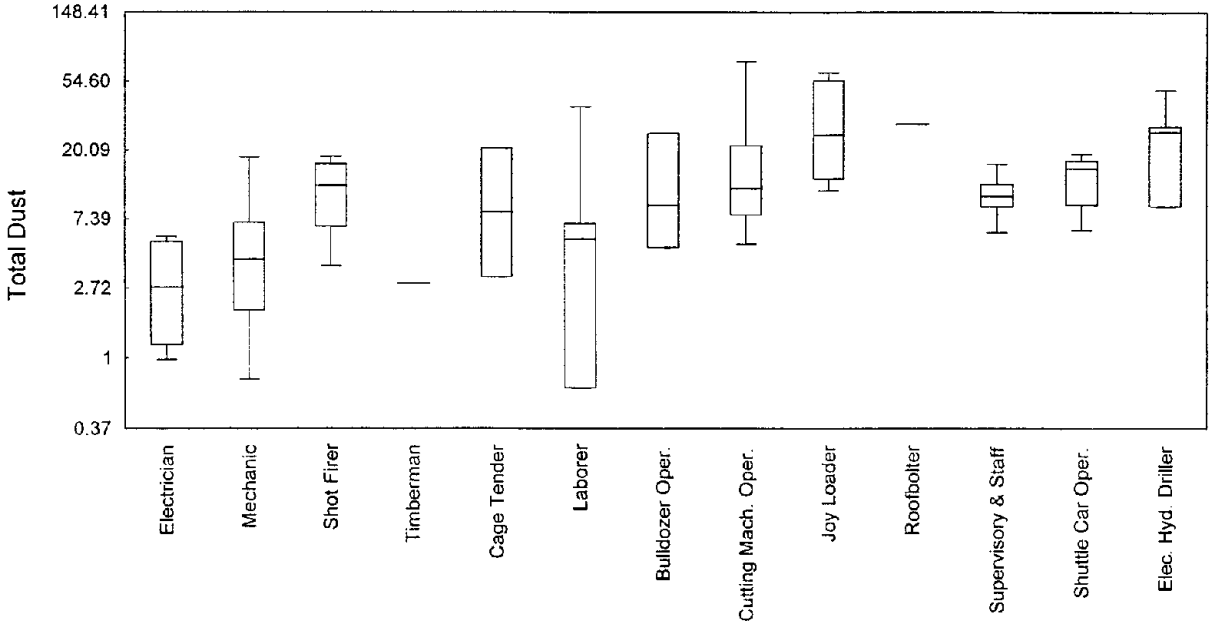


Figure F.14. Distribution of Total Dust (exp(ln(total dust))) by Job Title for Mine Number 18

(At Time of Sampling)

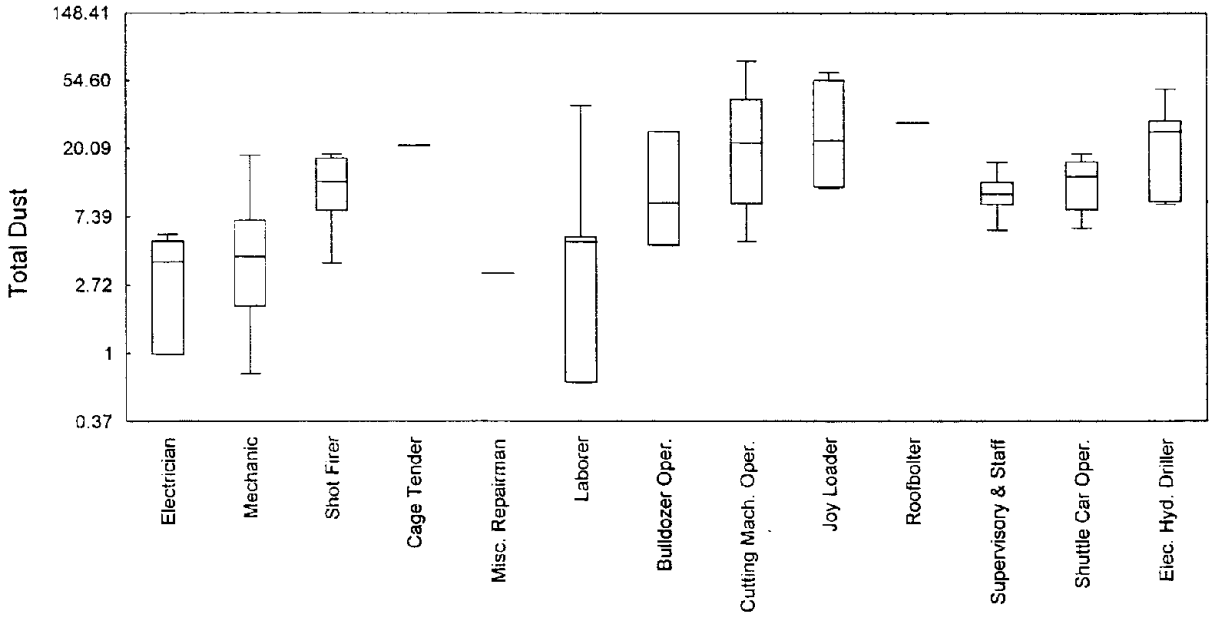


Figure F.15. Distribution of NO_2 (exp(ln(NO_2))) by Job Title for Mine Number 18
(Personnel Files)

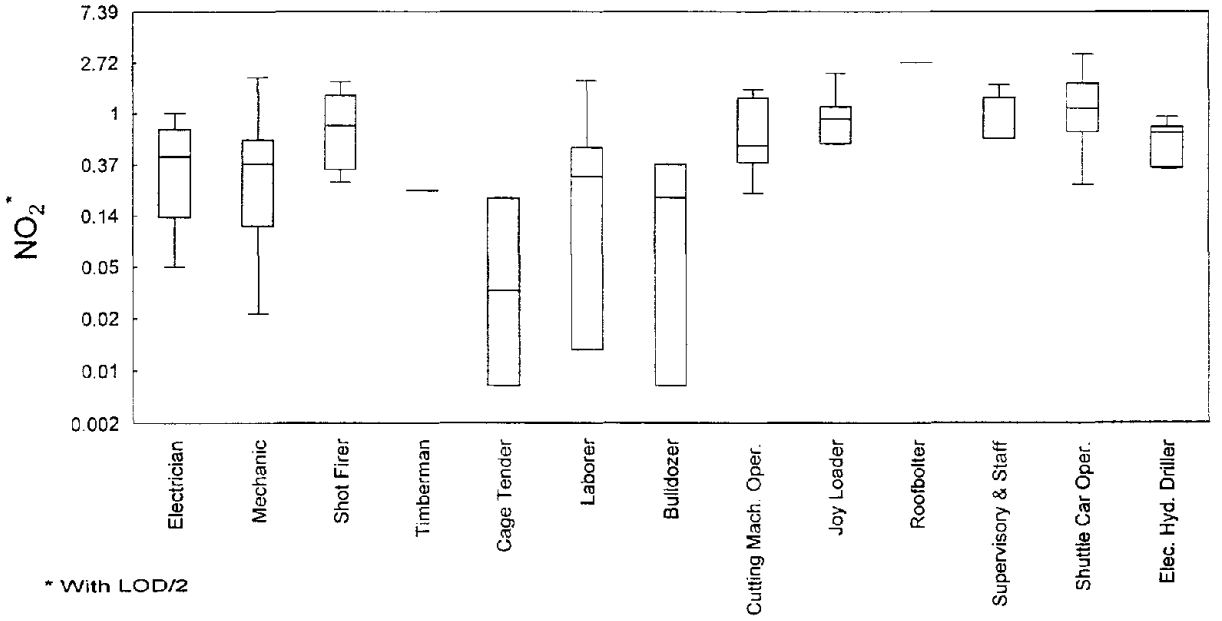


Figure F.16. Distribution of NO_2 (exp(ln(NO_2))) by Job Title for Mine Number 18
(At Time of Sampling)

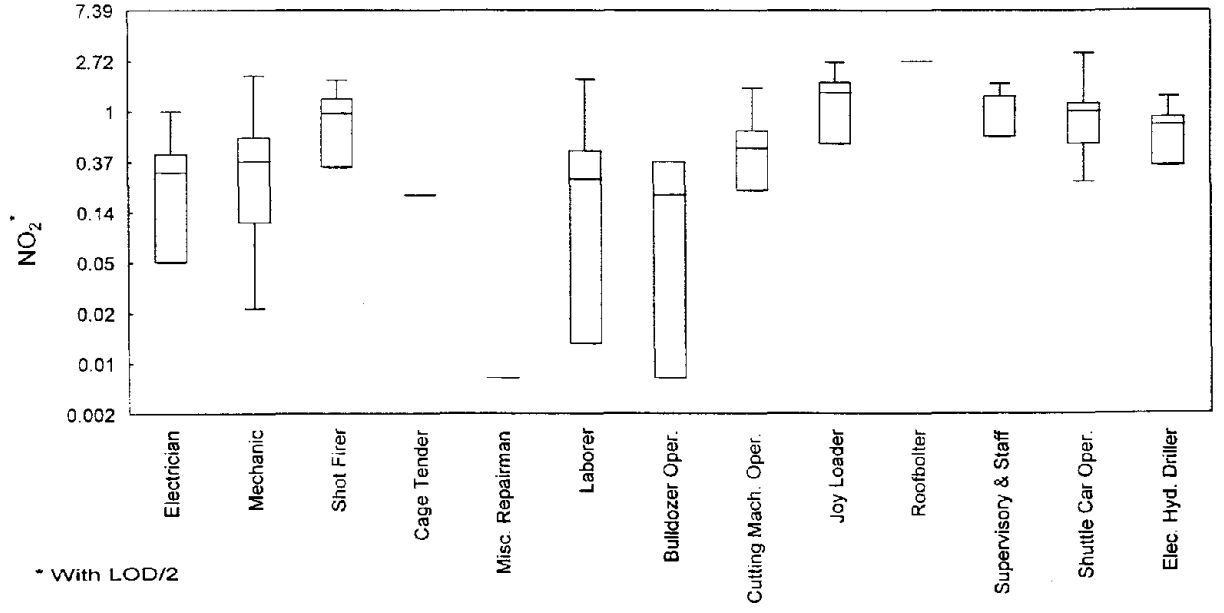


Figure F.17. Distribution of Percent Quartz (exp(ln(%qrtz))) by Job Title for Mine Number 18
(Personnel Files)

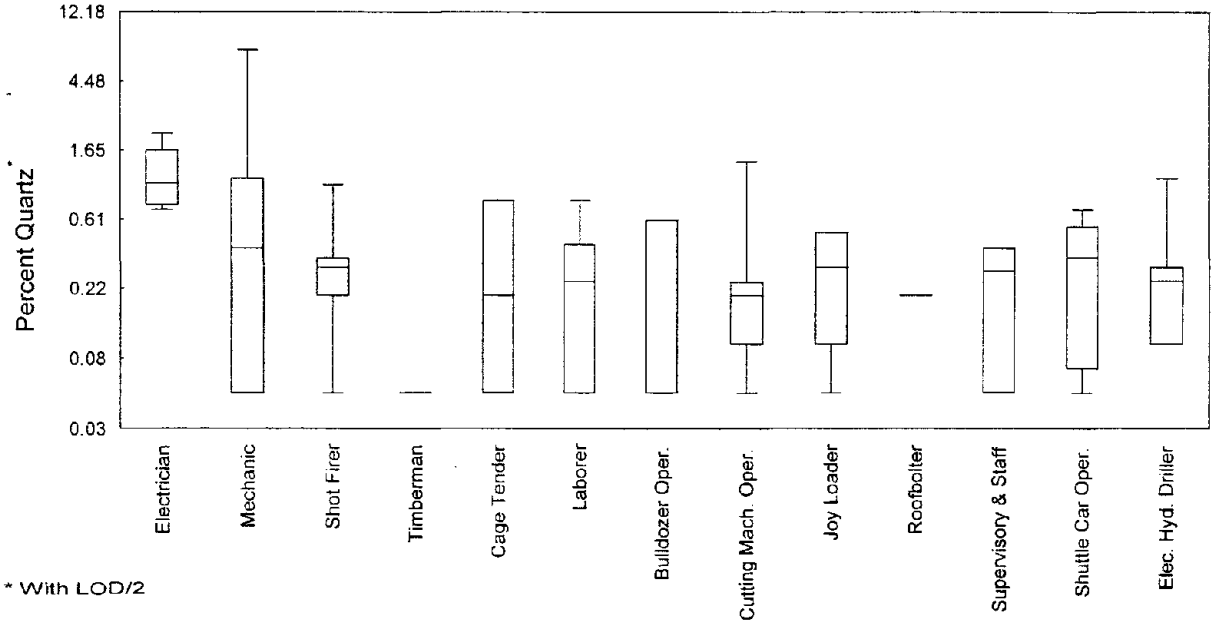


Figure F.18. Distribution of Percent Quartz (exp(ln(%qrtz))) by Job Title for Mine Number 18
(At Time of Sampling)

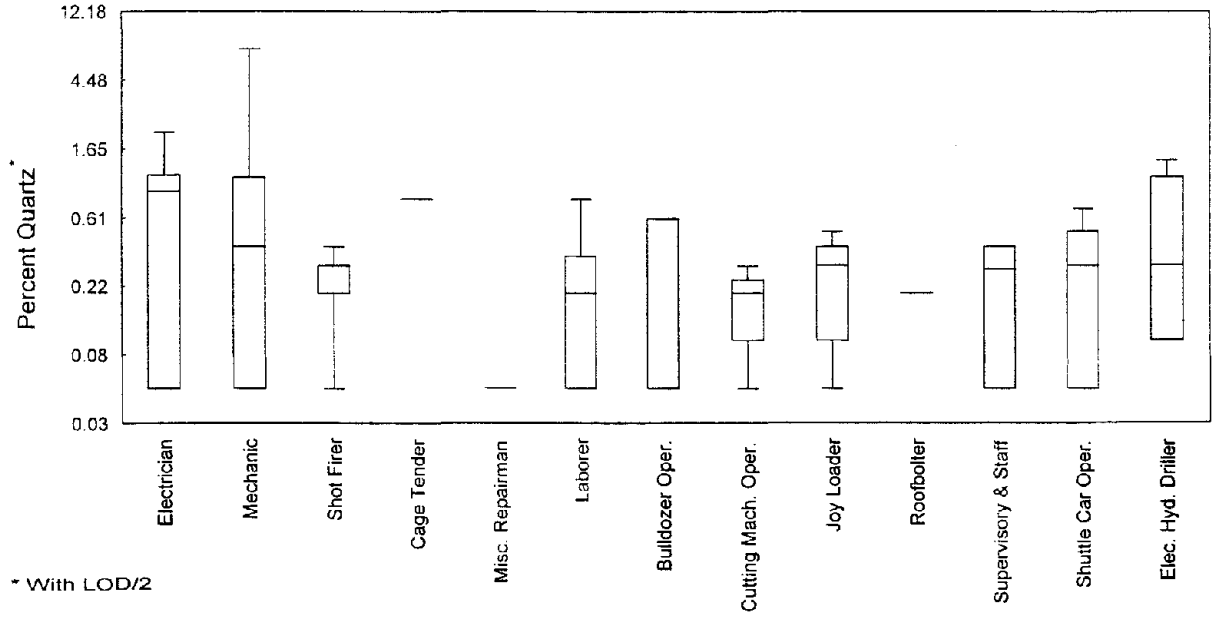


Figure F.19. Distribution of Total Dust (exp(ln(total dust))) by Job Title for Mine Number 19
(Personnel Files)

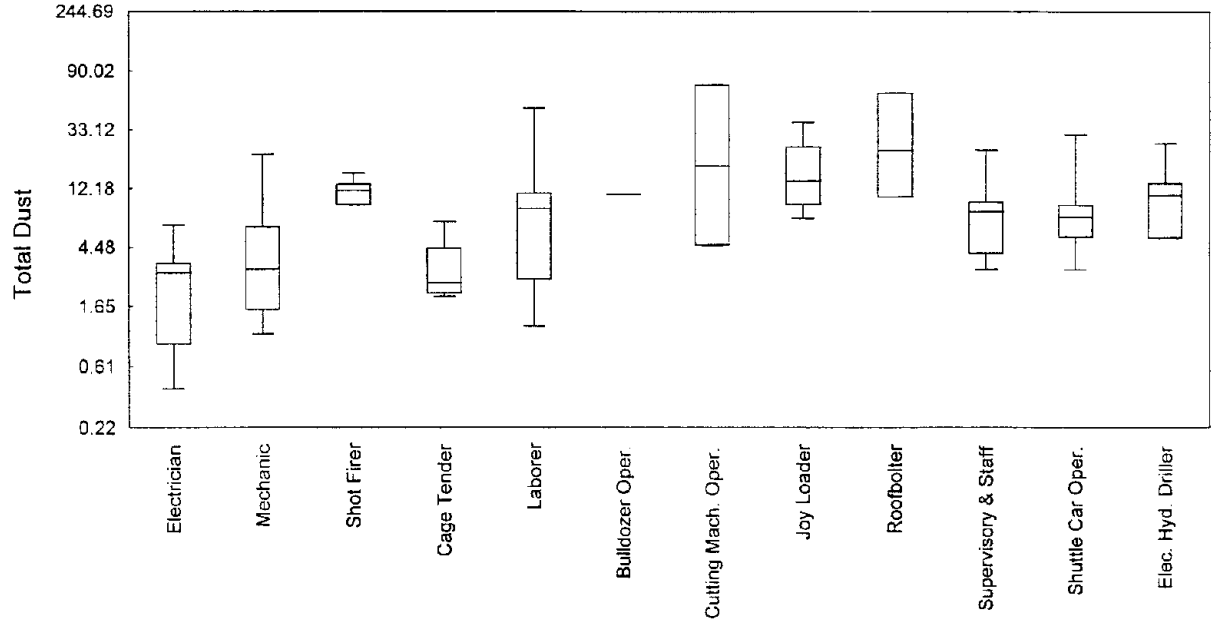


Figure F.20. Distribution of Total Dust (exp(ln(total dust))) by Job Title for Mine Number 19
(At Time of Sampling)

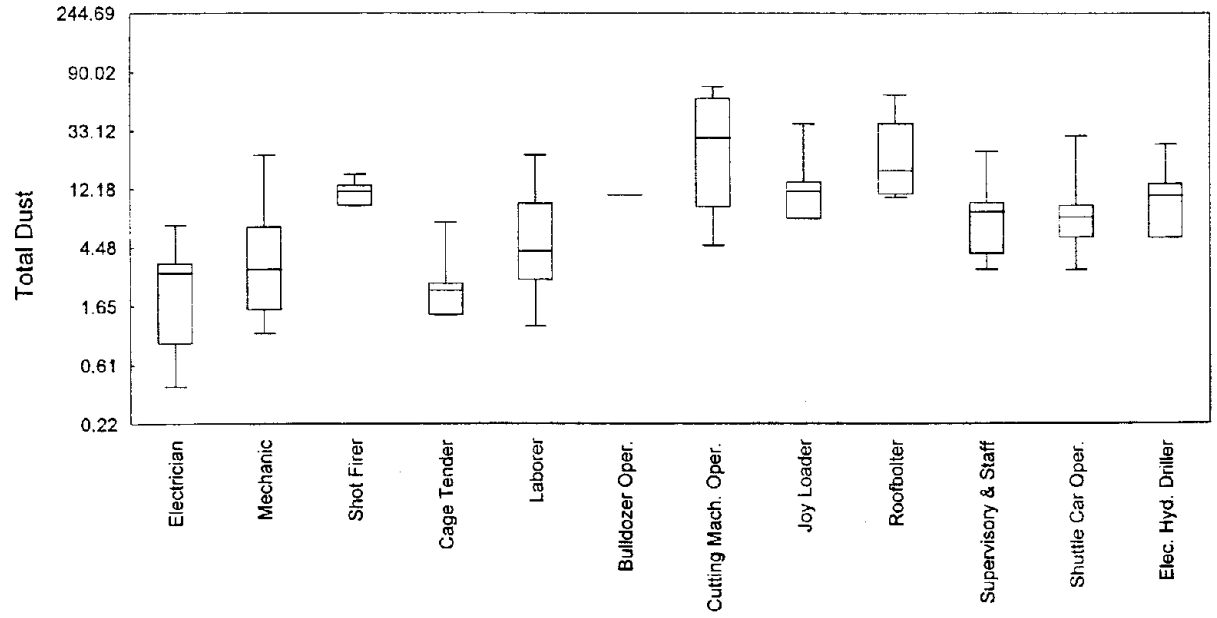


Figure F.21. Distribution of NO_2 (exp(ln(NO_2))) by JobTitle for Mine Number 19
(Personnel Files)

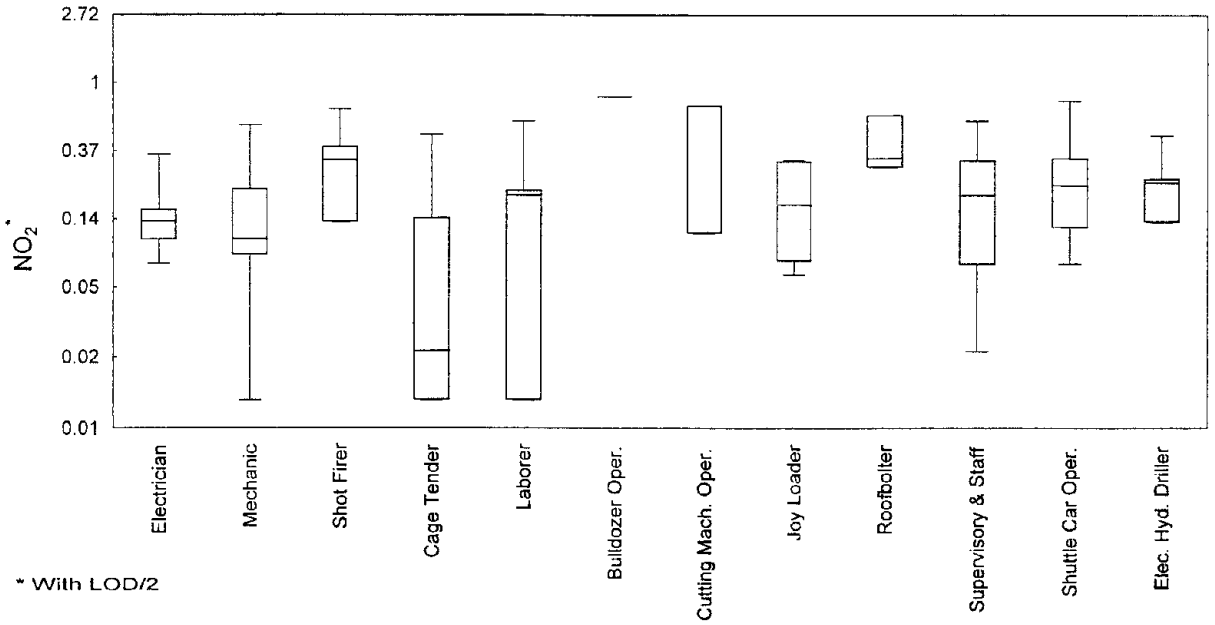


Figure F.22. Distribution of NO_2 (exp(ln(NO_2))) by Job Title for Mine Number 19
(At Time of Sampling)

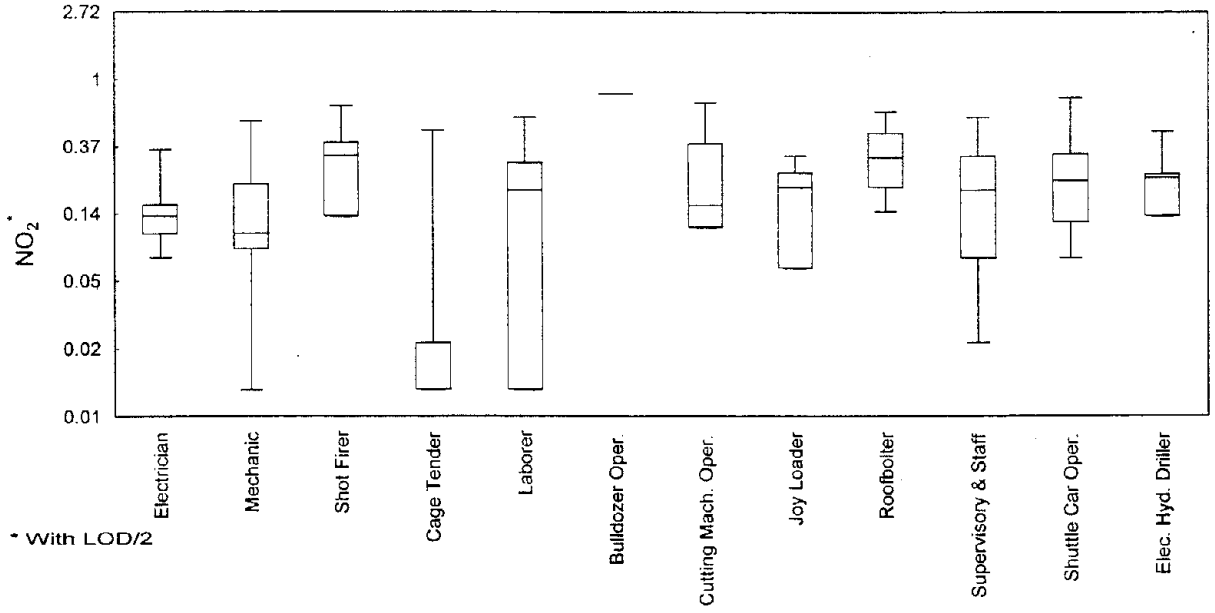


Figure F.23. Distribution of Percent Quartz (exp(ln(%qrtz))) by Job Title for Mine Number 19

(Personnel Files)

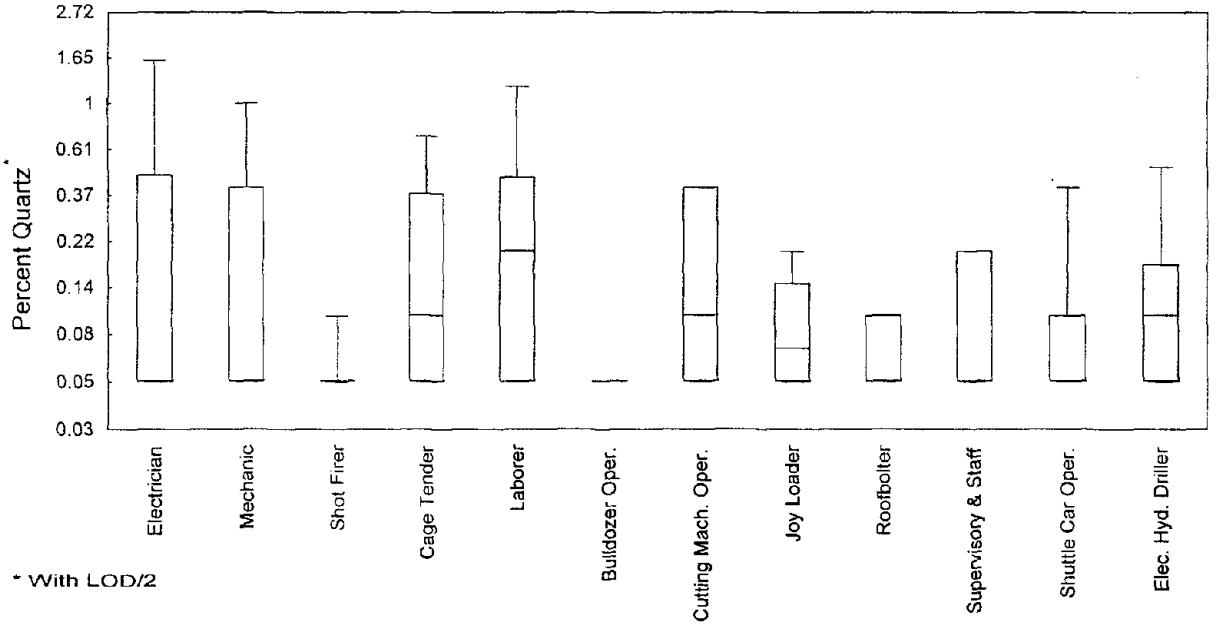


Figure F.24. Distribution of Percent Quartz (exp(ln(%qrtz))) by Job Title for Mine Number 19

(At Time of Sampling)

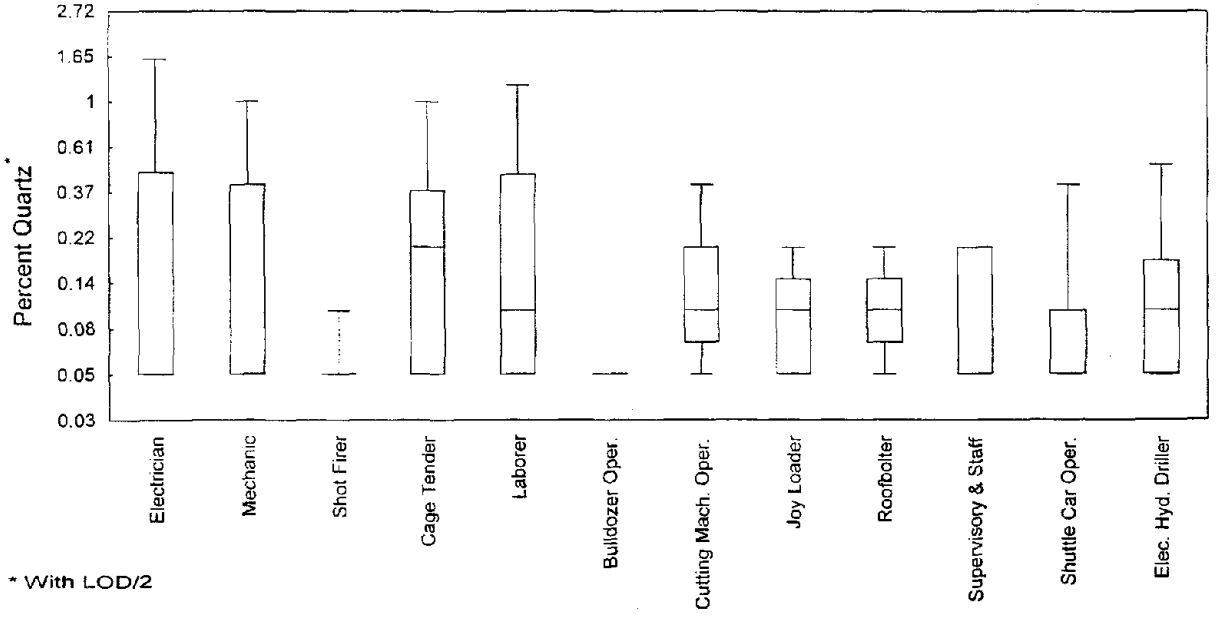


Figure F.25. Distribution of Total Dust (exp(ln(total dust))) by Job Title for Mine Number 21

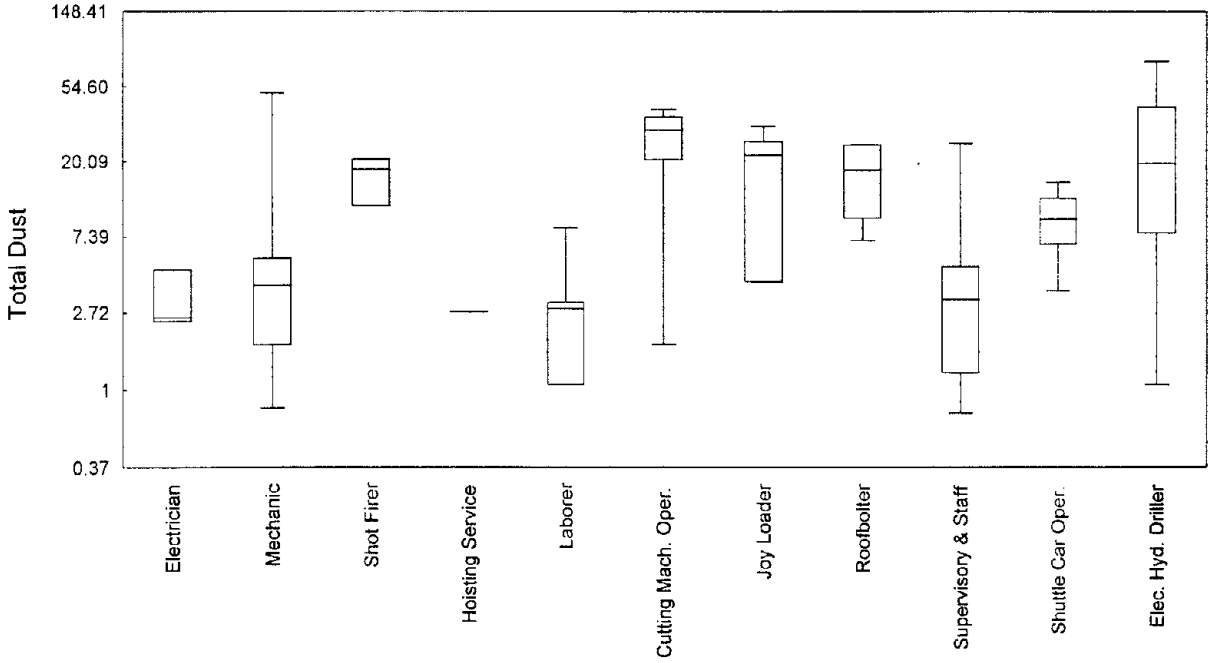


Figure F.26. Distribution of NO_2 by Job Title for Mine Number 21

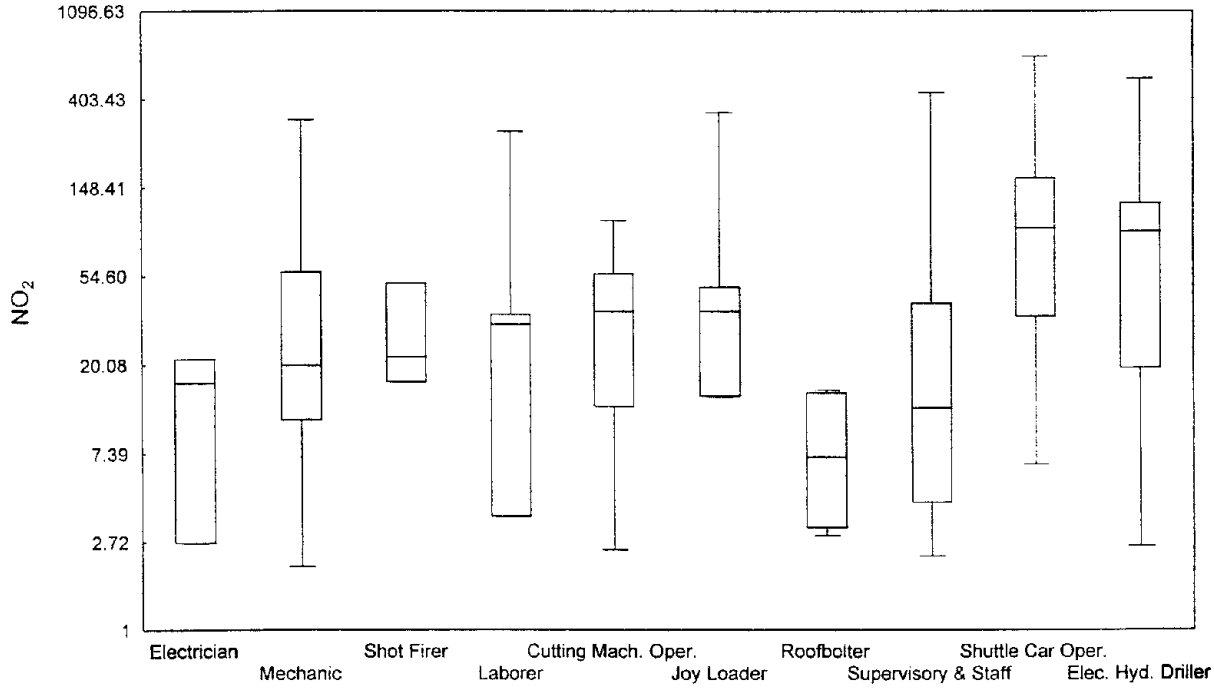
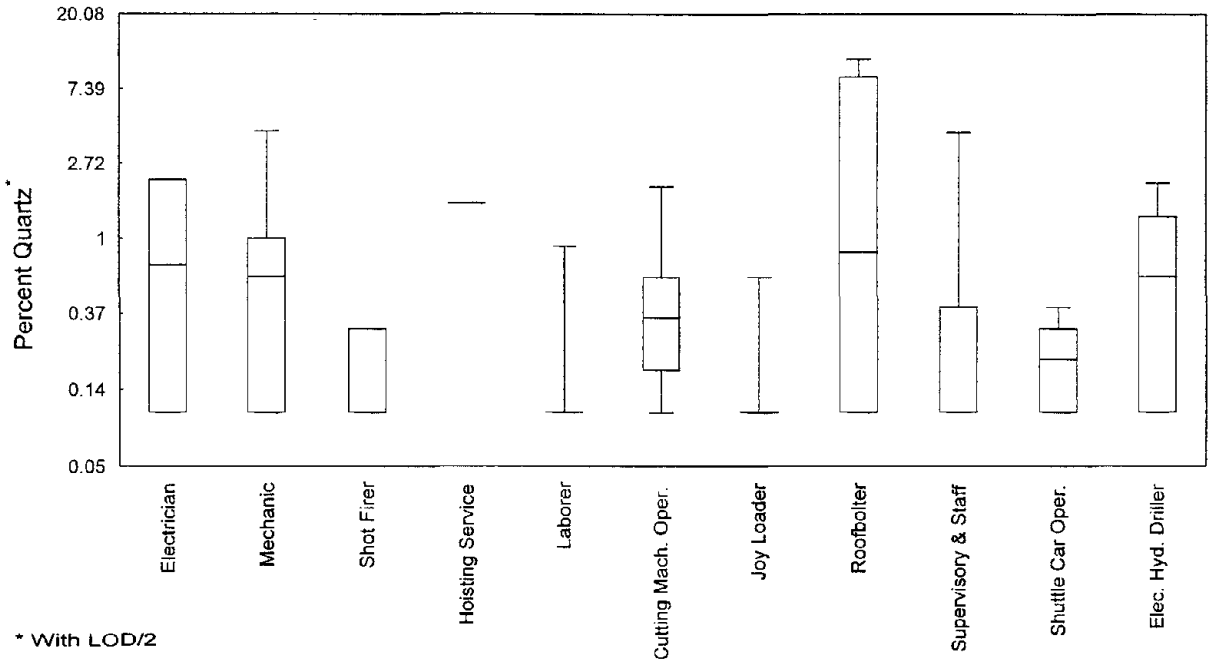


Figure F.27. Distribution of Percent Quartz (exp(ln(%qrtz))) by Job Title for Mine Number 21



DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
CENTERS FOR DISEASE CONTROL AND PREVENTION
ATLANTA, GEORGIA 30333

MEMBERSHIP

The Committee was composed of the following members in Fiscal Year (FY) 1997:

Jacqueline Agnew, Ph.D.
Johns Hopkins School of Hygiene
and Public Health
615 North Wolfe Street
Room 7503
Baltimore, MD 21205

Joseph D. Brain, S.D.
Cecil K. And Philip Drinker
Professor, Environmental Physiology
Harvard University School of
Public Health
665 Huntington Avenue
Boston, MA 02115

Linda H. Clever, M.D., F.A.C.P.
Chairman, Department of Occupational
Health
California Pacific Medical Center
P.O. Box 7999
San Francisco, CA 94120

Mark R. Cullen, M.D.
Occupational and Environmental Program
Yale University
135 College Street, 3rd Floor
New Haven, CT 06510

Letitia K. Davis, Sc.D.
Massachusetts Department of Public Health
250 Washington Street, 6th Floor
Boston, MA 02108

John M. Dement, Ph.D.
Associate Professor
Division of Occupational and
Environmental Medicine
Duke University Medical Center
P.O. Box 2914
Durham, NC 27710

Ellen A. Eisen, Sc.D.
Department of Work Environment
College of Engineering
University of Massachusetts
Lowell, MA 01854

Arthur L. Frank, M.D., Ph.D.
Associate Director for Medical Education
Professor of Medicine
University of Texas Health Center at Tyler
P.O. Box 2003
Tyler, TX 75710

Eric Frumin, Director
Occupational Safety and Health Department
Union of Needletrades, Industrial
and Textile Employees (UNITE)
275 7th Avenue, 6th Floor
New York, NY 10001

Gwendolyn P. Keita, Ph.D.
American Psychological Association
750 First Street, N.E.
Washington, D.C. 20003-4242

David P. Rall, Ph.D.
5302 Reno Road, N.W.
Washington, D.C. 20015

Philip J. Landrigan, M.D.
Department of Community Medicine
Box 1057
Mount Sinai School of Medicine
One Gustave L. Levy Place
New York, NY 10029

Martin Sepulveda, M.D.
IBM Corporation, P.O. Box 100
Route 100
Somers, NY 10578

Rosemary K. Sokas, M.D.
George Washington University
2300 K Street, N.W. #301
Washington, D.C.

Benjamin Y.H. Liu, Ph.D.
Director
Environmental Division
Mechanical Engineering Department
University of Minnesota
111 Church Street, S.E.
Minneapolis, MN 55455

James A. Merchant, M.D., Dr.P.H. (Chair)
Professor of Preventive and
Internal Medicine
Director of Agricultural Medicine and
Occupational Health
College of Medicine, University of Iowa
100 Oakdale Campus #124 AMRF
Iowa City, IA 52242-5000

Rafael J. Moure-Eraso, Ph.D.
Work Environment Department
College of Engineering
University of Massachusetts
One University Avenue
Lowell, MA 01854

Chaya S. Piotrkowski, Ph.D.
Professor
Fordham University
Graduate School of Social Service
113 W. 60th Street
New York, NY 10023-7479

Robert C. Spear, Ph.D.
University of California
School of Public Health
140 Warren Hall
Berkeley, CA 94720

Note: Shortly after the January 97 meeting, Phil Landrigan and Rosie Sokas resigned (both had accepted Federal employment and the BSC charter does not provide for membership to include federal employees). Thus, starting with the April meeting and continuing to today, we have only 13 of 15 authorized members.

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