Exhibit 99

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TESTIMONY OF HANS WEILL, M.D.

OSHA HEARINGS ON THE PROPOSED RULE ON OCCUPATIONAL EXPOSURE TO ASBESTOS

JUNE 19, 1984

My name is Hans Weill and I am Professor of Medicine and Chief of the Pulmonary Disease Division at the Tulane Medical Center in New Orleans. I direct an interdisciplinary unit engaged in the investigation of occupational lung diseases, with current research projects dealing with the wide spectrum of mineral and organic dusts, and chemical vapors and gases in the workplace. I and my colleagues have studied the respiratory effects of asbestos exposure, during the past fifteen years.

I have served as president of the American Thoracic Society, the medical and scientific arm of the American Lung Association, and as currently the chairman of the Pulmonary Disease Advisory Committee of the National Heart, Lung and Blood Institute (NIH). Our research has been supported primarily through federal funds (eg NIH and NIOSH). My colleagues and I are continuing our investigations of the morbidity and mortality associated with occupational exposure to asbestos in the manufacture of asbestos cement building products. During this year I am in residence at the Brookings Institution in Washington, as a Fellow in Science and Public Policy. My work at Brookings involves an examination of the use of science in policy decision-making as it relates to the asbestos-related diseases, including the regulation of workplace exposures.

## ASBESTOS AND ITS EFFECT ON HEALTH

Under certain conditions of asbestos mining, milling, manufacturing and end-product use, an airborne dust cloud is generated and fibers may be inhaled by proximate workers. Fiber deposition, clearance, and tissue persistence are primary determinants of the types and severity of the diseases which may ultimately result from asbestos exposure. These factors are in turn importantly influenced by fiber type and dimension (diameter and length). Dust concentration and length of exposure, which determine the total or cumulative lung tissue burden or "dose" are quantitatively related to measures of the disease outcomes. Where differences in disease risk have been associated with parts of the industry studied, such risk gradients are likely to be related to the factors enumerated above.

Very thin fibers (generally <1 micron in diameter) are most likely to be deposited deep within the lungs and relatively long fibers (>8 microns) are most likely to be retained for long periods of time in lung tissue. The distributions of fiber physical dimensions almost certainly relate closely to the pathogenic potential of the asbestos exposure.

Thin or "respirable" fibers are carried down the branching air conducting system of the lungs, the bronchial tree. They are most likely to deposit in the smallest such conducting tubes, called respiratory bronchioles and alveolar ducts. These

structures not only conduct air into the lungs but also participate in the exchange of oxygen (uptake) and carbon dioxide (removal), the primary function of the lungs. The fibers reaching these deep recesses of the lungs have escaped the initial defense mechanisms which protect man against inhaled particles, motile projections (cilia) and a moving mucus layer on the inner bronchial surface which propel the fibers upward where they can be swallowed or expectorated.

Fibers once deposited in the lung may then be engulfed by scavenger cells (phagocytes or macrophages) but when the fibers are long, the phagocytosis is likely to be incomplete. When successful, engulfed particles may be eliminated by the muco-ciliary escalator or by transport to the regional lymph nodes. They may also be coated by protein and iron from the tissue and remain for long periods of time as "asbestos bodies", perhaps having l ot their pathogenic potential. Remaining asbestos fibers embedded in the tissue lead to the development of disease over many years.

Two primary tissue responses result from asbestos exposure: scarring (fibrosis, called asbestosis when the lung is involved) and cancer (carcinogenesis). Fibrosis begins in the peripheral and lower zones of the lungs, a reflection no doubt of the pattern of heaviest mineral deposition. Gradually, the process becomes disseminated throughout the lungs. A characteristic of the fibrotic lung is that it is contracted (smaller than normal), stiff (poorly compliant) and deficient in its ability to exchange

gases. The precise biological mechanism is incompletely understood. Macrophages which only partially ingest a fiber are damaged and release substances which induce other cells (fibroblasts) to produce and lay down scar (collagen). Once initiated, the fibrogenic process is progressive, even after exposure to asbestos ceases. Generalized or focal fibrosis (the latter called plaques) of the lining of the lungs (pleura) is also a common consequence of asbestos exposure, but with rare exceptions results in no functional impairment and should be considered only as an indicator of exposure. Significant asbestosis is recognized only as the result of occupational exposure to asbestos; pleural fibrosis may result from environmental (eg neighborhood or household) exposures. It is not likely that clinically important chronic airways obstruction (as seen with chronic bronchitis and emphysema) is the primary consequence of asbestos exposure.

Important increase in risk for developing two malignant tumors has been repeatedly demonstrated in asbestos exposed individuals: lung cancer and mesothelioma, the latter a cancer of the pleural or peritoneal (abdominal lining) surface. The carcinogenic mechanism in either case is poorly understood, but certain relationships have emerged, perhaps giving some clues to pathogenesis.

Risk for lung cancer is greatest in those exposed individuals who have also developed asbestosis. Indeed such

evidence which is available suggests that an exposure dose which detectably increases the risk of lung cancer will also result in asbestosis in a similarly exposed population. Smoking increases the lung cancer risk in a synergistic manner. Evidence that specific lung cancer cell types or lung location of the tumor are particularly associated with asbestos exposure, is not convincing. Recent investigations suggest that asbestos may act as a tumor promotor following the independent initiation of the process. It should be borne in mind that there is a substantial background of this tumor in the general population (130,000 cases in the U.S.par year) and there are no specific indicators of asbestos causation. Excess risk for the development of this tumor has been recognized only in occupationally exposed populations. All asbestos fiber types have been associated with excess lung cancer risk.

Fortunately, mesothelioma is a rare tumor (approximately 1500 cases in the U.S. annually), since it is almost invariably fatal, no effective therapy being available. Most cases are caused by exposure to asbestos, the proportion being variable in the reported retrospective reviews of series of cases. Minimum causative exposure dose is likely to be shorter and perhaps lower than for the other asbestos associated diseases, probably explaining the considerable number of reported cases with domiciliary and neighborhood exposure. It has been suggested that asbestos acts as an initiator of this tumor. Exposures early in life are apt to increase the risk greatly since it appears that the risk increases by the power of three or four with time since

first exposure. Evidence for a gradient of risk in relation to fiber type is strongest for mesothelioma, exposure to crocidolite or amosite being much more likely to result in the development of this tumor than chrysotile.

Usually, two or more decades elapse from first exposure before either the non-malignant respiratory effects or the malignant intrathoracic tumors become clinically evident; the "latency period". Other cancers have been less consistently found to be associated with asbestos exposure: most prominently gastrointestinal and laryngeal; less often ovarian and kidney. The epidemiologic evidence is equivocal and the animal studies are not at all supportive of these putative relationships.

## DEVELOPMENT OF KNOWLEDGE REGARDING THE HEALTH EFFECTS

A quarter of a century following the commercial introduction of asbestos, the first case of lung fibrosis, later called asbestosis, was recognized and reported to the British government. By the 1920's and early 1930's asbestosis risk was clearly recognized in asbestos textile manufacturing on both sides of the Atlantic, as reflected by the medical literature. That this risk was dose-related was shown by USPHS studies in the late 1930's, leading to the first suggestion of a dust exposure level intended to result in no risk of disease (threshold limit value). Asbestosis risk in users of asbestos-containing products was regarded as minimal as the result of a report on New England shipyard workers, published in the mid 1940's, and it was not

until twenty years later that studies of insulators showed substantial evidence of lung fibrosis in this occupational group.

Case reports in the United Kingdom, Germany and the United States in the 1930's first suggested that an increased number of lung cancers seemed to occur in workers with asbestosis. An autopsy study in the U.K. supporting this association was published in the late 1940's and, in 1955, the first epidemiologic study of workers in asbestos textile manufacturing clearly showed increased lung cancer risk in this exposed population. Excess lung cancer risk in mining and milling was established in the late 1960's and early 1970's and in insulators in the early 1960's. The relationship between asbestos exposure and lung cancer risk was accepted earlier in the U.K. and Europe than it was in the United States, where the scientific community was not uniformly convinced of the risk until the 1960's.

A rare and highly malignant tumor of the pleural and peritoneal surfaces, mesothelioma, was associated with exposure to asbestos as the result of important observations in South Africa, reported in 1960. Workers and others exposed to crocidolite asbestos in and near the mines in the Northwest Cape were found to have (and die of) this form of cancer with alarming frequency. Subsequently, mesothelioma risk was confirmed in manufacturing and end-product use of asbestos around the world. The relevance of non-occupational exposures in the causation of this tumor became increasingly apparent. Exposures were often

short with a long latency period of generally two to four decades.

## SCIENTIFIC ISSUES IN QUANTITATIVE ASSESSMENT OF RISK

Quantitative risk assessment underlies the rational management of that risk by regulatory policy. The greatest public confidence in decision-making to reduce an environmental or occupational risk results when the data used are the product of well designed and conducted studies of relevant human populations. This type of investigation is called epidemiology, the investigation of populations in order to detect the distribution and determinants of disease. The strength of epidemiologic evidence varies with study design, some types of studies being more "powerful" than others. When an occupational hazard has been identified, useful epidemiologic study results will determine the quantitative relationship between the dose of exposure to the causative agent and the risk of the adverse health response in the exposed population. The product is the exposure-response relationship, which together with a valid estimate of the size of the exposed population, the extent of that exposure and accurate indicators of the disease outcome, give the characterization of the risk. It will, of course, also provide levels or cumulative doses of exposure which can be expected to result in a predetermined risk, including one which is considered to be "reasonable" or "acceptable". Optimally, the exposure-response relationship for a specific agent will be generalizable for all circumstances of exposure; often varying

relationships are found for differing conditions. It has been primarily since 1970 that valid quantitative assessment of the risk has been accomplished for varying circumstances of asbestos exposure in the workplace. Although such data for asbestos exposure is probably more complete than for any other occupational exposure, it should not be assumed that all uncertainty regarding the exposure-response relationships has been resolved; it has not.

At present, exposure-response relationships have been established for asbestos-related disease in mining and milling; and in various parts of the manufacturing of asbestos-containing products, such as textiles, asbestos-cement, and friction materials. Since contemporaneous measures of exposure are not available for workers exposed to the dust of end-product use, such as insulators and shipyard employees, any quantitative risk analysis based on exposure-response estimates will be less reliable than when these data are accessible. Attempts have, however, been made to estimate "average" exposures for these industries, which have then been used to construct a slope based on certain additional assumptions, eg. the shape of the exposure-response curve for lung cancer being linear without a threshold. Such a slope will be based on one exposure point and will contain considerable uncertainty, being clearly inferior to slopes constructed from multiple exposure-specific risk points, which show an exposure-related risk gradient.

Regulatory decision-making for the prevention of asbestos-

related diseases would be substantially simpler if the quantitative risk analyses gave similar results irrespective of the industrial process, type(s) of asbestos fiber to which the worker had been exposed and the specific asbestos-induced disease. The evidence indicates that such comparability is not the case. An additional complicating aspect in the use of existing quantitative estimates of risk is that all general environmental levels of asbestos exposure and most recent occupational exposures will be lower than any of the observations or estimates of past exposures which have been used to derive exposure-response relationships. In order to assess risk at the relevant levels of exposure which are of current concern, extrapolation of the relationship to these levels below which "hard" data are available, becomes necessary. Further, even if epidemiologic data were available on health experience at currently relevant low exposures (after the appropriate latency period for the disease appearance has elapsed), the sensitivity of the methods of disease detection, particularly cause-specific mortality, is, in general, not likely to be sufficient to reliably measure this level of risk.

Therefore, specific considerations necessary to generate quantitative risk assessments for asbestos exposure include: the shape of the exposure-response curve, differing risk estimates for the various exposure-related diseases, the influence of industry component and fiber type, the form and quality of the disease response and exposure data, and the role of non-

occupational potential modifiers of the dose-response relationship (eg. smoking). These factors will often not be independent, or indeed, distinguishable in their effect on the risk analysis. It is, however, incumbent on scientists to take these and other potentially influencing factors into account and clearly present the assumptions which have been made so that an optimal characterization of the risk will emerge.

## INFLUENCE OF DISEASE OUTCOME ON SHAPE OF THE CURVE

While the shape of the dose-response curve for asbestosis cannot be determined with certainty, it is clear that this fibrotic effect is dose-related, perhaps linearly, and whether a threshold exists may very well depend on the response indicator chosen. The clinical and other features of this fibrosing disease of the lung include abnormal chest sounds heard on auscultation (rales or crackles); shortness of breath which is excessive for the level of physical activity in which the individual is engaged; rarely, deformity of the tips of the fingers and toes (including the nails) called clubbing; small linear or irregular shadows on the chest x-ray film; derangement of the function of the lung, most often reduced volumes and disturbance of gas (oxygen) exchange; and certain patterns of abnormality detected on microscopic examination of lung tissue (fibrosis and asbestos bodies), usually obtained by surgical biopsy or autopsy. All of these features are non-specific but in practice, for clinical (and legal) purposes, an exposure history and characteristic x-ray pattern are sufficient for making a diagnosis. In studies of

exposed populations, relationships have been sought by assessment of the response using a predetermined combination of these features of the disease (eg. at least three), one of them (eg. the x-ray pattern) after other possible influencing factors have been taken into account), certification by an administrative body for purposes of compensation, or mortality data which depend on the death certificate diagnoses. These approaches have varying degrees of limitation, including observer variability, and the subsequent uncertainty must be borne in mind when evaluating resulting data.

A final complicating aspect in the development of exposure-response information on asbestosis is that it is a slowly progressive disorder which may (and frequently does) continue to worsen after exposure ceases. Varying studies have looked at the prevalence or incidence of the disease as the biologic response variable. Prevalence is a measure of the frequency of the condition in a population at one point in time and is the result of both the rate at which the condition is appearing in the population under study, as well as survival of the affected individuals. Incidence is the number of new cases which are being recognized (ie. diagnosed) during a specified period of time, usually per year. The latter is generally regarded as being the more informative measure, since it more fully expresses the risk.

There is little disagreement that reduced recent exposures have resulted in lower risk of asbestosis and less severe disease. When asbestosis is statistically detectable, it is not

likely to impair function, produce symptoms or reduce longevity, and therefore, risk analysis for asbestosis has been relegated to a position of lesser importance in contrast to that for the malignant consequences of asbestos exposure.

Quantitative risk analysis is quite a different matter for the malignant diseases due to asbestos exposure. As regards the shape of the dose-response slope, an operational judgement is based on the conclusion that there is currently no available evidence that convincin ly proves that the slope is not linear, crossing the risk axis at the origin. This assumption (as made in the OSHA risk analysis) is justified from the observations at moderate and high levels of exposure that generally indicate linearity, which when extended downward to levels of exposure below which observations are available, are not inconsistent with linear low dose extrapolation. Taking into account the relative insensitivity of population studies to detect slight increases in risk of malignant disease, it seems unlikely that epidemiology will ever provide evidence regarding the shape of the curve at its low end or whether a threshold exists. However, the possibility that such evidence might emerge from animal models of carcinogenesis is not excluded. At present, it seems reasonable (prudent), that for purposes of policy development, the linear-at-low dose, no threshold model be employed.

Of the the two major malignant diseases caused by asbestos exposure, lung cancer and mesothelioma, the former is highly

prevalent in the general population (background) and is most often not the result of asbestos or other occupational exposure. The latter is, however, rare and most often caused by asbestos exposure. While available data indicate that both conditions are dose-related, quantitative aspects of asbestos-induced lung cancer risk are better known than those for mesothelioma, owing primarily to the relative frequency of these tumors and, perhaps, to differential accuracy of diagnosis in the past. Best evidence at present indicates that while the lung cancer risk curve is linear in relation to dose, mesothelioma incidence also seems to increase with the third (or slightly greater) power of the time interval since first exposure, in addition to being proportionately related to intensity of exposure.

For the reasons already given (differences in background incidence of the two types of cancer), lung cancer risk is usually expressed as a ratio of observed cases, in a population or exposure sub-group, to expected number of cases in a non-exposed comparison group, such as the U.S. population. Depending on the specific study design, this may be expressed in standardized mortality ratios, risk ratios or relative risk. Since the occurrence of mesothelioma in an asbestos exposed individual is considered to be causally related to the exposure, risk is expressed in actual number of cases. No convincing dose-response relationships have been reported for other cancers (eg. gastrointestinal).

## INFLUENCE OF INDUSTRY SEGMENT ON THE RELATIONSHIP

The relationships between dose of asbestos exposure and lung cancer risk, as determined by various epidemiologic studies, vary considerably, according to the segment of the industry. Where valid dose-response data are available, there is a gradient of risk (highest to lowest) from the manufacture of asbestos textiles to asbestos-cement and other asbestos-containing products and finally to mining and milling, and friction materials manufacture, where the slope is least steep. As indicated previously, asbestos pathogenic potential seems to be related to fiber dimension, namely diameter and length. Longer, thinner fibers are probably most hazardous, this type of physical configuration being most likely in the textile industry. Other factors, as yet unrecognized, may also be important in this regard. Accurate dose-response relationships are not known for end-product use, since minimal exposure data for relevant time periods are available. There is no evidence to suggest that mesothelioma risk varies significantly by industrial activity.

## EFFECT OF FIBER TYPE EXPOSURE

There is a growing consensus that amphiboles are more hazardous than chrysotile. The evidence is based primarily on studies of exposed human populations; animal exposure data are not confirmatory of this risk gradient. The most impressive gradients of risk by fiber type have been demonstrated for mesothelioma. In mining of chrysotile and crocidolite and in the

manufacture of textiles, friction materials, and gas masks in World War II, the mesothelioma experience of exposed workers has been strikingly less favorable in those who were exposed to amphiboles alone or in combination with chrysotile, in contrast to populations exposed to chrysotile alone. For example, in the study of South Carolina asbestos textile workers, where the lung cancer risk was among the highest of any demonstrated, the mesothelioma risk was minimal. These workers were exposed only to chrysotile asbestos. Mesotheliomas have been relatively rare in miners and millers of chrysotile asbestos in the Province of Quebec, in contrast to the experience of those occupationally and environmentally exposed to the dust of the crocidolite mines of the Northwest Cape of South Africa and Australia.

During the Second World War, gas mask filters were manufactured using asbestos. Apparently, crocidolite was considered superior for this purpose and was therefore utilized in making masks for military personnel; chrysotile was employed in the production of civilian gas masks. In workers engaged in this wartime activity in Nottingham, U.K., and in Ottawa, Canada, a substantial differential mesothelioma risk has now become apparent, following the expected several decades of latency time for the development of these tumors. Again, most of the mesotheliomas are occurring in those individuals previously exposed to crocidolite.

If one examines the twenty major epidemiologic studies of mortality in asbestos-exposed workers which have been published

to date (or are about to be), mesothelioma experience can be compared by fiber type exposure in relation to excess lung cancer risk, expressed as observed cases minus the expected. The latter might be thought of as a surrogate measure of exposure, allowing for assessment of mesothelioma risk after differences in level of fiber exposure have been taken into account. The highest average ratio for mesothelioma/excess lung cancer appears in the crocidolite exposed populations, followed by mixed fiber exposures (usually including crocidolite), then amosite exposure, and the lowest ratio found in studies of populations exposed to chrysotile alone (see appended table).

The evidence on fiber type influence on risk of asbestosis and lung cancer is far less convincing, primarily because it is much more limited in extent. Where such evidence has been sought, it has generally suggested that, as with mesothelioma, these risks tend to be greater if there has been exposure to amphiboles.

There are biologically plausible reasons why fiber-specific risk differentials might exist. Reference has previously been made to the importance of fiber dimension in pathogenesis. It is likely, for example, that a cloud of asbestos dust contains a higher proportion of respirable "carcinogenic" fibers if crocidolite is present (fibers >8 microns in length and <1 micron in diameter). Crocidolite might therefore be more likely to be deposited in the deep portions of the lung and migrate more

easily to the pleural surfaces. Additionally, it has been recognized that chrysotile fibers do not have infinite tissue persistence. They are known to be soluble to some extent, probably due to leaching of their magnesium. Workers with many years of predominantly chrysotile exposure may, on elegant mineralogic examination of their lungs, have numbers of these fibers similar to unexposed controls, clearly indicating that lung tissue analysis is not an accurate indicator of chrysotile exposure. This is not the case with amphibole exposure, these fibers generally being retained in the tissue for very long periods, as demonstrated by comparable lung tissue analysis. These differences in tissue persistence may wholly or partially explain the observations in human exposed populations cited above. Non-confirmation of fiber type differences in animal experiments may be related to the much shorter life span, not allowing the effects of varying tissue persistence to be expressed.

## ASSESSING THE QUALITY OF THE DATA

Risk assessment inferences must ultimately take into account the form and quality of the data upon which the analysis is based, among other factors. Quantification of the risk depends first upon the quality, the form and the temporal appropriateness of the exposure information in the group for whom risk is being related to exposure. These factors have varied considerably among the studies which are available for possible risk analysis.

In the 1960's and before, airborne dust measures in workplaces in which there has been asbestos exposure, have quantified total particulates (all dust), not just asbestos fibers. Since the relationship between fibers and other particulates is known to vary under differing conditions, exposure to asbestos during those years can only be estimated by applying ratios to convert total particulates to fiber levels. These conversion ratios have at times been empirically determined under more recent conditions and assumed not to have changed much from the past (although levels of exposure certainly have), or they have been estimated without direct measurement. The number of actual dust measurements which can be used for exposure reconstruction is very limited for work sites before the 1950's, an era with obvious influence on health risk being observed in recent years, due to the latency effect, already discussed.

Measurement of airborne fibers (of a certain dimension) became prevalent in the U.S. only in the late 1960's. While helping to estimate past exposures in terms of fibers, the actual asbestos concentrations determined can be validly correlated only with the health experience now evolving in exposed workers. However, epidemiologists appropriately utilize the best available data, while at the same time fully presenting the limitations of these data. And so they have done, with individual exposure dose estimates being derived from total and asbestos dust measurements for whatever time periods for which they are available. Taken into account is the time of measurement, job history of members

of the study cohort, and conversion ratios for expression of dose in fiber levels (the way in which standards for workplace exposures are now expressed), and useful exposure-response relationships have been generated.

Quantification of "dose" has generally been accomplished by estimating cumulative exposure, obtained from the product of dust concentration for a particular job at a specific time period and time at that concentration, with the resulting products over the working lifetime being summed. There are two major assumptions in this procedure, neither presently scientifically provable. First, that a heavy exposure over a short time is likely to result in the same risk as a low or moderate level exposure over a longer period of time, if the product is the same. There is certainly evidence that both duration and concentration of exposure influence risk, but the precise quantitative contribution of each is not known. Secondly, since the mineral has a long residence period in lung tissue and presumably continues to exert its pathogenic effect after exposure ceases, some weighting of exposure dose by residence or time since first exposure might seem appropriate. However, a valid way of doing this has not been demonstrated. In spite of the difficulties summarized, these curves, in the main, appear quite plausible, essentially always showing dose-relatedness of the effect, and bear reasonable relationship, one curve to another, when the conditions lead to the expectation of concordance.

Least satisfactory for purposes of quantitative risk analysis is when the absence of dust measurements during the appropriate time periods makes it impossible to attempt to reconstruct individual estimates of exposure over the worker's lifetime. As a substitute, applying one or more average exposure estimates to large segments of the study population may easily lead to misleading overall quantitative estimates of risk, since there is likely to have been considerable variability among those considered to have the same exposure. Additionally, when average levels of exposure are used for study groups, a gradient of risk by dose of exposure cannot emerge and cannot, therefore, provide a degree of validation by showing that the risk is indeed, dose-related. This is the situation for the studies of insulator and shipyard workers. While providing qualitative information on asbestos-associated diseases, these studies have limited utility in producing reliable exposure-response relationships upon which to set workplace standards. This is particularly regrettable from a public health point of view, since the important asbestos exposures in the recent past and in the future are likely to be in those whose work puts them in contact with asbestos-containing materials, as in the construction trades.

The state of affairs regarding data quality is substantially better on the other side of the exposure-response relationship, ascertainment and quantification of the adverse effect on health. There too, however, uncertainties exist. Primary reliance for risk assessment in the malignant diseases associated with asbestos exposure is placed on analysis of age and cause-specific

mortality. Comparison populations should be appropriate for the cohort under study, and difficult choices have been encountered when county, state and U.S. cancer rates have differed. Expected death rates must be obtained for the comparable era because of secular trends (changes) in mortality experience in the general population. The study population vital status should be known for a high proportion of the cohort and sufficient follow-up time must be allowed to accurately reflect the risk of long latency diseases, such as occupationally induced neoplasms. Death certificate diagnoses have a margin of error, but attempts to obtain further information regarding diagnosis after death, such as review of pathologic material, have not generally altered study results or interpretation. Incidence (new cases occurring per unit of time) of tumors may not be accurately reflected in mortality data. Unfortunately, in the case of lung cancer and mesothelioma, the primary tumors of interest in asbestos exposed populations, their very poor cure rates result in a satisfactory approximation of incidence by mortality statistics. Uncertainty regarding the risk of death from a specific cause in an exposure category will obviously be affected by the number of cases in that cell, the number of cases expected for that group and indirectly by the total size of the study population. Smaller numbers widen the confidence limits, and consequently reduce the precision of the exposure-response slope. While these potential limitations may seem to be overwhelming, in fact, extremely useful risk analyses have been possible and there is amazingly broad-based confidence in the estimates.

Mortality data are not useful in fully quantifying the risk of asbestos-induced lung fibrosis (asbestosis). Affected workers may die with asbestosis but not of it, in which case it is not likely to appear on the death certificate as the primary cause of death. In contract, sensitivity of detecting early evidence of asbestosis in a living exposed population has increased substantially in recent years. Standardization in the reading of abnormalities consistent with asbestosis by radiographic (x-ray) classification has been especially facilitated by continuing improvement in the international classification now widely used (ILO). The randomized reading of films of exposed workers, without any information regarding the individual whose film is being classified, including exposure, results in quite good reproducibility of readings or at least consistency in "over or under-reading". Since much of the asbestosis being seen now is the result of lower dust levels in the past two decades, the films are likely to be classified in the lower categories of profusion of small opacities (fewer shadows meaning less severe disease). As is frequently the case with biological measurements, it is at these lower limits of disease detection that inter- and intra-observer variability is greatest. Again, it is gratifying to know that in spite of these recognized problems, excellent exposure-response relationships have resulted from the radiographic classification described.

While the chest x-ray indirectly measures structural or anatomical alterations in the lung, pulmonary function testing

assesses the effect that injury to the lung tissue has had on the capacity of the respiratory system to perform its basic functions of delivering "fresh" air to the distal lung sacs (alveoli) for the purpose of exchanging gases between the lung and blood; ie. oxygenation. Asbestosis will, at some stage, interfere with this normal function, but so may other injurious influences (eg. smoking, allergy). As with x-ray reading in the dust diseases, pulmonary function testing has become increasingly standardized with better quality control and improved apparatus. When using functional measurements as indicators of a dust effect, which has resulted in quite satisfactory exposure-response relationships, other potential confounding influences must be taken into account in the statistical analyses. It appears, at least on the basis of population-based data, that the chest x-ray and lung function are equally sensitive in the early detection of asbestosis, although in an individual case, one method may reveal abnormality before the other.

Exposure-response relationships have been reported using as the biologic response indicator either a constellation of clinical findings to define asbestosis, or certification by a worker's compensation panel or board. These two studies, from the United Kingdom and Ontario, used incidence of asbestosis and found different quantitative relationships with estimates of past asbestos exposure. The variation in results may have been due to differences in length of maximum follow-up (more cases being expected when longer follow-up is possible); differing criteria

by the two certifying bodies for compensation awards; [illegible] to differences in methods of determining past exposure (q[illegible] likely).

How do the exposure-response relationships for the major disease outcomes of asbestos exposure differ? With very few exceptions, specific curves are not available for mesothelioma but indirect evidence strongly suggests that exposure dose resulting in this tumor may certainly be short, if not low. Presumably, the exposure-response curve would be expected to be steeper than that for lung cancer risk, under the same circumstances, although for most mortality studies of working populations exposed to asbestos, the number of excess lung cancer cases is likely to exceed the frequency of mesothelioma. This is undoubtedly influenced by factors other than cumulative dose of asbestos, such as the low background incidence in the general population and absence of the important influence of smoking on mesothelioma risk. The power relationship of mesothelioma risk with time since first exposure also results in attenuated risk when exposure first occurs later in life. Population data are not now available, nor are they likely to become so in the future, to set a permissible exposure limit in the workplace based on exposure-response relationships for this tumor.

Although past standards for asbestos have generally been based on asbestosis risk, this is no longer the case. The current emphasis in asbestos risk analysis is firmly focused on the malignant consequences of this exposure. It therefore becomes

relevant to consider data which provide information regarding the relative risk of asbestosis and excess lung cancer at tolerable levels of exposure. Before doing this, it must first be clear what outcome is being measured. As previously indicated, exposure-response relationships for malignancy are based on cause-specific mortality, ie. deaths from the tumor under consideration. Since I have already suggested that for asbestosis, mortality studies are not likely to fully express the risk, other evidence must be sought. Since the diagnosis can be made at a rather early stage, and the disease is slowly progressive, it should be recognized that there will be a substantial number of exposed workers with some evidence of asbestosis, which is not likely to result in functional impairment or reduced longevity. What may be less apparent is that limited but rather convincing evidence indicates that in populations or subgroups exposed to levels of asbestos in which there has been detectable excess lung cancer risk, asbestosis is also likely to be demonstrable. To my knowledge, there is no evidence to the contrary, ie, exposure levels which have been shown to protect from asbestosis but where excess lung cancer risk is demonstrated. The policy implication which follows is that work[illegible] standards should reasonably be based on either asbestosis or lung cancer risk if the former is assessed using sensitive methodology, and, in both instances, evaluating these health effects after the appropriate latency time has elapsed.

Clearly, the most important of the known personal factors that effect the disease outcomes caused by asbestos exposure, is smoking. The situation differs for each of the three major conditions: asbestosis, lung cancer and mesothelioma. There is no evidence that smoking causes diffuse lung fibrosis of the type that would be expected to be confused structurally or functionally with asbestosis. However, there is indeed evidence from population studies that low level profusion of small opacities on the chest x-ray, of the type seen in asbestosis, may be associated with cigarette smoking. In that sense, smoking is a confounding influencing factor which must be taken into account when relationships are sought between asbestos exposure and radiographic evidence of asbestosis. This is not, of course, the same as saying that smoking is a contributing cause of asbestosis: in my view, it is not.

Smoking does, however, frequently cause chronic lung disease in the general population. These conditions are often generically called chronic obstructive lung disease, comprising primarily chronic bronchitis and pulmonary emphysema. When they coexist with asbestosis they can be expected to enhance the functional effect of the occupational disease, but the dual exposure is not likely to have contributed substantially to clinically significant airways obstruction. One often reads in the press that asbestosis is a chronic lung disease which is "similar to emphysema". In fact, the clinical, radiographic, pulmonary function (physiologic) and anatomic features of asbestosis and emphysema could not be more distinct and should not be easily

confused. In terms of non-malignant respiratory disease, both asbestos and smoking are important causes. While they cause different diseases, the effects of smoking on the airways and their function, as well as the x-ray, must be taken into account when considering the relationship between asbestos exposure and diffuse lung disease. This can quite readily be accomplished in population studies but is more difficult to sort out in individual cases.

It is for lung cancer that the synergism between cigarette smoking and asbestos exposure has appropriately received the greatest attention. Our information on the relationship between these two causal factors comes from the relatively few mortality studies of asbestos-exposed workers where smoking histories are available. The data indicate that the interaction is more than additive and may very well be multiplicative (the product of the two risk factors, eg. in the insulator studies, a risk ratio of 10 for smoking, 5 for asbestos, 50 for the combination of both factors acting together). While it is clear that the extent and prevalence of smoking in a study population, its various exposure groups, and the comparison or control group, can have an extremely important effect on lung cancer exposure-response curves, there is insufficient information available to allow smoking to be used in quantitative risk assessment for asbestos-related lung cancer. At present, in epidemiologic research, we can at best attempt to characterize the smoking habits of the study cohort and assess comparability in regard to this

influencing variable between the study population and the comparison (unexposed) population, and between sub-groups of the cohort which have been stratified by level of exposure. While the relative contribution of asbestos exposure and smoking can, with sufficient information, be estimated in populations, it is extremely difficult to do so in an individual with this tumor, where both causal factors have been present.

Brief comment seems appropriate regarding the possible significance of immunologic abnormalities which have been found in the blood and cells of asbestos-exposed or diseased individuals. Investigators have hoped that such findings might provide information regarding pathogenesis of these conditions and, perhaps, be useful in predicting an adverse response in exposed workers. To date it seems that these immunologic findings are most likely to be the consequence of tissue injury and appropriately called "epi-phenomena", being of little value in either identifying the susceptible worker, correlating with the risk or severity of disease or providing factors to be taken into account in generating dose-response relationships.

In discussing risk analysis, I have reviewed the considerable influence of a variety of factors which are likely to affect the measured extent to which asbestos causes malignant and non-malignant diseases. These include, but are undoubtedly not limited to: segment of the industry in which asbestos is used; fiber type; physical dimension of the fiber; choice of a comparison population; differences in follow-up time in the study

population; smoking habits of the study and control populations, and between exposure groups in the study cohort; quality and form of the dust exposure data and such assumptions as conversion ratios for total particulates to fibers; and criteria for ascertainment of the health response under study. In spite of these important sources of variability, we know of no other occupational disease for which more complete exposure-response data are available from human population studies.

## THE OSHA PROPOSAL FOR AN ASBESTOS STANDARD

OSHA has relied on a quantitative risk assessment for asbestos exposure which is based on currently accepted methodology. Most, if not all, of the variables discussed have been considered and it is very similar to the risk analysis produced by the Chronic Hazard Advisory Panel (CHAP) on Asbestos of CPSC. There is not, nor is it likely that there ever would be, complete agreement on all underlying assumptions and decisions, concerning, most notably: choice of studies for determination of exposure-response slopes for lung cancer and mesothelioma risk, differential risk related to fiber type, risk gradient for differing portions of the industry, and whether to include risk of gastrointestinal neoplasms in the analysis.

However, on such issues, compromise and functional consensus has generally evolved. No significant differences have emerged in

choice of models. At most, changes in the assumptions which I and my colleagues might make in the risk analysis, would result only in lowering the estimated excess deaths (lifetime risk) resulting from asbestos exposures by a factor of two, under identical conditions of age at first exposure, duration of employment and level of exposure, and, if risk gradients by fiber type and process are ignored. With those caveats, and considering all of the uncertainties readily conceded in the process, I can accept the OSHA risk assessment as reasonable and supportable.

The regulatory choice of a permissible exposure limit (PEL) for asbestos clearly extends beyond the scope of biomedical science or public health. Such factors as technological and economic feasibility (available approaches and cost of risk reduction), measurement validity, work practices, personal respiratory protection (versus engineering controls), and evaluation of comparative risks all require broader input. These considerations aside, the residual risks associated with 45 years of exposure to 0.2 or 0.5 fibers/ml., under conditions of fiber type use and processes constituting past exposures (7 and 17 excess deaths per 1,000 workers over their lifetime in the OSHA risk assessment), are not easily defended by those committed to reduction of workplace hazards. Obviously, the non-health related factors cannot be ignored, as evidenced by the OSHA proposal. Also, there are additional considerations.

I do not believe that all exposures to asbestos result in the same risk to workers. I have reviewed the evidence which

indicates that exposure to different fiber types, and in distinct parts of the industry, has produced differing levels of risk in workers. I believe that this scientific evidence is strong, although by its nature, never conclusive. It clearly falls under the rubric: "best available", upon which policy decisions are most often taken. There will, of course, be considerations, falling within the expertise of disciplines other than biomedical science, which will, and should, contribute to the regulatory policy which OSHA is formulating, in part based on these hearings.

However, I would be remiss in my responsibility in this rule-making procedure if I did not provide judgments on policy, which I have concluded are supported by the available scientific evidence, once again re-stating my recognition that final decisions will be based on broader considerations. I find it difficult to justify the continued use of amphibole asbestos, crocidolite and amosite, when it can be avoided. Demolition and other construction exposures to these fibers will, of course, be unavoidable in the foreseeable future. Unacceptable risk has been demonstrated or estimated at levels of exposure that are probably lower than can practically be attained, so that discontinuing all use of these fibers in the manufacture of new products and similar introduction in the workplace, should be the desired regulatory objective. How this is to be achieved, I will leave to others.

As indicated, the evidence also allows evaluating the risk gradients which have emerged in relation to process. Mining and milling exposures are not germane to these proceedings, and will not be considered further. The manufacture of asbestos textiles probably results in an unreasonably high risk and should be regulated most stringently among manufacturing processes, perhaps to the point where continuing viability of this portion of the industry is doubtful.

Under the above assumptions of exclusive chrysotile use and manufacturing processes limited essentially to asbestos-cement products and friction materials, the analysis of risk cited previously should be considered as a substantial over-estimate. It then becomes probable that a PEL for asbestos of 0.5 fibers/ml. would result in a potential risk which is not unreasonable. Should a differential regulatory approach be rejected, adequate risk reduction might not be achieved, even at a PEL of 0.2 fibers/ml., although non-scientific reasons may make this limit the lowest "feasible" one which can be promulgated.

It should not go unnoticed that other governments, based on the conclusions of their advisory groups that all asbestos risks were not the same, have opted to follow this course. Of recent interest in this regard, because of its thoughtful, thorough and overall exemplary approach to public policy in the asbestos-related disease issues, is the superb report, published in May of this year, of the Ontario Royal Commission on Asbestos. In addition to Canada, other countries regulating asbestos according

to fiber type are: Australia, Belgium, Denmark, Ireland, the United Kingdom, Italy, Japan, New Zealand and Norway. Even in the U.S., we have recognized differing risks by banning a number of uses of asbestos (eg. spraying of asbestos insulation). Further, OSHA has previously set different PEL's for separate parts of the cotton industry, and, indeed, for different jobs in the textile portion of that industry. I would encourage the Agency to consider a similar approach to the regulation of asbestos.

## MEDICAL SURVEILLANCE OF ASBESTOS EXPOSED WORKERS

Finally, I would like to direct my attention briefly to rules covering medical surveillance of exposed workers. As indicated earlier, asbestosis is a slowly progressive disease, and, due to the substantially lower exposures of the last two decades, the extent or severity of this disorder is currently, and will continue to be in the future, most often minimal to modest. Specific treatment is not available and short term incremental exposures at current operating levels are not likely to have a measurable effect on progression of the disease. For these reasons, and the general precept that all unnecessary irradiation should be avoided, I recommend that chest x-ray films be mandated at a three yearly interval, a change from the current requirement of yearly films. I would not favor this change if medical evidence showed that annual chest films significantly improve prognosis when a malignant tumor is discovered on routine x-ray surveillance---this is, unfortunately, not the case.

The eliciting of respiratory symptoms and performance of spirometry are less of benefit in asbestos-exposed workers because of their specificity (they are non-specific in regard to exposure-related effects, primarily asbestosis) than for their use in making the worker and his physician aware of a departure from respiratory health, most commonly chronic airways obstruction, due to chronic bronchitis or pulmonary emphysema. While annual symptom inventory and pulmonary function tests should be considered part of good general medical surveillance from middle age on, particularly in high risk groups, such as smokers, the major benefit to be expected is the successful counselling of the early obstructed individual to discontinue smoking. For the limited purposes of occupational health monitoring, these procedures could also be required only once every three years. No new additional medical procedures are justifiably mandated for inclusion, at this time, in the surveillance program.

# END DOCUMENT

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3/18/85