ESTIMATES OF THE FRACTION OF CANCER IN THE UNITED STATES RELATED TO OCCUPATIONAL FACTORS

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This statement addresses the question: "What is the best estimate of the fraction of cancer incidence (or deaths) in the United States that is reasonable to attribute to occupational exposure in the present, and in the forseeable future?" Previously published estimates of this fraction have been as low as 1% to 5% for past data [reviews by Higginson (1-3), Wynder and Gori (4), and Doll (5)] and as high as 10% to 15% [see the discussion by Cole (6)]. All these estimates are somewhat speculative and several were seriously incomplete or deficient. Most are now out of date. If recent evidence is considered and if the full consequences of occupational exposures in the present and recent past are taken into account, estimates of at least 20% appear much more reasonable, and may even be conservative. These estimates refer to the near term and the future.

Four Pitfalls

Four general problems confound attempts to answer this question.

(a) Incomplete data. Few industries have been investigated adequately for evaluating the possible occurrence of occupationally related cancers. Because of the insensitivity of epidemiologic surveys and various difficulties in conducting them (7), only agents and industrial processes which lead to rather large excess incidences have been identified to date. The International Agency for Research on Cancer (IARC) has an ongoing program to review data on chemicals for potential carcinogenic effects. To date, some 368 chemicals and industrial processess have been reviewed. According to a recent

summary of the results of this program (8), some 26 chemicals or industrial processess have been identified as associated with increased risk of cancer in man (Table 1). This list includes a number of drugs and chemicals to which there is little or no occupational exposure in the United States. Only 8 or 9 of the 26 substances and processes listed in Table 1 involve exposure to large numbers of workers. By way of contrast, some 221 chemicals or mixtures were identified in the same survey as carcinogenic to one or more animal species. Although there is some occupational exposure to the majority of these 221 substances, epidemiological and case studies were in all cases either lacking, or inadequate to determine whether or not the substances are associated with excess cancer incidence in exposed human populations (8). Thus, adequate data are available for only a very small fraction of the substances and industrial processes which pose potential risks to exposed workers. Although it is possible that all the major hazards have already been identified, there is little reason to believe this without much more extensive epidemiologic investigations. In fact, many new processes and materials have been introduced in recent years. Some of these could be as hazardous or more hazardous than those used in the past.

(b) <u>The fallacy of "one effect - one cause" explanations</u>. Wynder and Gori (4) offered a tentative allocation of cancer incidence in the United States attributable to specific environmental factors. Their estimates of the proportions of cancers attributable to diet, tobacco, radiation, occupation, alcohol, and exogenous hormones have been widely quoted. However, a major difficulty with their procedures is they have classified all cancers under single "causes."

whereas cancer appears to be a disease of interactions. The initiation and development of cancer is a multi-phased, multi-causal process in which both external and internal factors act, probably at each of several stages, before frank, clinical cancer appears. It is likely that many, if not most, cancers are influenced by two or more different external factors acting simultaneously or sequentially. Thus, alcohol by itself appears to be a minor cause of cancer--but alcohol combined with cigarette smoking leads to risks 15 times higher than those experienced by non-smoking non-drinkers. If a drinker smoker develops cancer of the oral cavity, to which "cause" should it be attributed? Drinking or smoking? If we could correctly identify the proportions of cancer incidence "attributable to" each of the classes of environmental factors considered by Wynder and Gori, the sum of these percentages would be considerably higher than 100. One of the best-studied examples of interaction between exogenous agents is that between asbestos and cigarette smoke in inducing lung cancer (9). Most lung cancers "attributable to" asbestos are probably simultaneously "attributable to" smoking. If current theories of a multi-casual process are correct, it seems likely that a large fraction of cancers which at first appear to be "attributable to" smoking should also be "attributable to" asbestos, radiation, and/or other occupational factors.

(c) Latent period, age, and duration of exposure. Most occupational carcinogens are characterized by "latent periods" of 10 to 50 years between the onset of exposure and the clinical appearance of tumors (7). This is consistent with a multi-stage process. When occupationally related cancers are detected, they usually reflect

exposures which started one or more decades in the past. Accurate numerical assessment is further complicated by the strong dependence of cancer incidence upon age and upon duration of exposure. Even in cases where and excess risk is detected within one or two decades, this dependence on age implies that most of the attributable cancers will not occur until later in the life span of the exposed workers, perhaps as much as 40 or 50 years after the first exposure. It is difficult to trace anyone for so long a time, and those epidemiological studies which do not follow people for a full lifetime are likely to underestimate lifetime risks. Most industrial-epidemiologic studies have not (and probably could not) follow a working population to its extinction. This problem is discussed in more detail in the Appendix, but a numerical example illustrates its importance. For many types of cancer, incidence increases approximately as the fourth or the fifth power of age (10); hence the cumulative number of cancers occurring in a population over a lifetime increases as the fifth or sixth power of age. If exposure to a carcinogen results in a constant multiplicative increase in risk at all ages, then the number of cancers occurring in an exposed group will similarly increase as the fifth or sixth power of age. Thus, for example, the number of attributable cancers occurring by age 50 would be only about one-fifth or one-sixth of that expected by age 70. For this reason epidemiological studies often enumerate only a small fraction of the total excess cancers attributable to an agent. Any overall assessment of the importance of occupational carcinogenesis should take this into account.

(d) Changes in exposure patterns. The dependence of cancer risk upon age and duration of exposure is further complicated by changes in patterns of exposure to potential carcinogens. Few, if any, workers are exposed throughout their entire working lives to the same chemical at similar concentrations. American workers change jobs fairly frequently; even within the same job, the chemicals to which a worker is exposed may be changed from time to time. By the time an occupationally related cancer develops, the workers will frequently have been exposed to different chemicals and may well have changed occupations. It is particularly difficult to make estimates of the consequences of present-day exposure, because the chemicals for which we have the best dose-response information are those which are generally recognized as carcinogenic. Several of them have been regulated, so that exposure to these chemicasl has been reduced; this leaves other carcinogens that are not well controlled.

Previous Attempts to Estimate the Importance of Occupational Carcinogenesis

In 1969, Higginson (1) tabulated estimates of "the extent to which occupational and cultural cancers have been recognized." He attributed to known occupational factors 1% of mouth cancers, 1-2% of lung cancers, 10% of bladder cancers and 2% of skin cancers. (No detailed development of these estimates was given, however.) Higginson limited his attributions to factors that "have been recognized," and the majority of cancers were assigned to "unknown" factors.

In 1976, Higginson and Muir (2) again estimated the impact of environmental factors in human cancer. They stated, again with few supporting details:

> "Although occupational cancers recognized so far provide some of the most satisfactory data for identifying external agents, the absolute number of cancers due to occupational exposures would appear to be relatively small, probably 1% to 3% of all cancers."

In 1977, Wynder and Gori (4) presented estimates of the "percent of cancer incidence in the United States attributable to specific environmental factors." It would appear from Figure 1 in their paper that their median estimates for the fraction of cancers attributable to occupational factors were 4% for men and 2% for women. Their explanation for these estimates was:

> "The data presently available are, at best, educated estimates of the relationship between specific cancers and specific occupational groups. Cole et al. (56) suggested that 20% of bladder cancers occurring in males in the Boston area are related to occupational exposure. In certain counties of New Jersey, the increased risk for this cancer appeared to be high among workers in certain chemical industries. Bailar (personal communication) estimated that the occupational contribution to total cancer incidence in males lies between 1 and 5%; and a similar estimate was made by Nelson (personal communication). General estimates of the percentage of all human cancers related to occupational exposure range between 1 and 10%. However, identification of specific high-risk groups, hazardous exposure levels, and related cancer incidence rates is yet to be determined."

In addition to the error of "one-effect, one-cause" thinking pointed out above, their reliance on "educated estimates," "personal communications," and "general estimates" makes the resulting conclusions tenuous. And again, of course, no attempt was made to estimate future consequences of past exposures.

In 1977, Doll (5) published a survey of the importance of environmental factors in human cancer in the U.K. He indicated his belief that occupational factors were of relatively small importance, but did not make a numerical estimate.

In 1977, Cole (6) estimated the fraction of cancer that is occupationally-induced to be less than 15% for men and less than 5% for women. He explained the basis for these estimates as follows:

> "I estimated that the occupationally-induced burden was less than 15% for men and less than 5% for women. The major causes of cancer deaths are cancers of the lung, the breast and the colon; and these are largely or totally non-occupationally induced. Lung cancer is 90% cigarette-smoking-induced; breast cancer is probably not at all occupationally induced; there may be some, probably small, occupational component in cancer of the rectum. Other sites such as cervix or ovary have a negligible occupational component, if any. The above listed sites account for about half of the cancer deaths. For other sites, it is difficult to assess the occupational component. However, even an 'occupationally-related' cancer like bladder cancer can be attributed directly to occupational exposures only about 25% of the time. With half the cancer essentially non-occupationally induced, and half the cancers occupationally-induced less than 25% of the time, a reasonable estimate seemed to be 15% for males."

This argument also assumes that a cancer which is related to a non-occupational factor cannot also be occupationally related. Cole's statement of the basis for his estimates makes it obvious that all these estimates contain a large element of uncertainty.

We conclude that the statement that no more than 1% to 5% of cancers in the United States are attributable to occupational factors is based on partial use of current knowledge, reflects the one-cause one-effect fallacy--and is not particularly useful for estimating

future risks. It is not even a correct reflection of the published estimates, which range up to 10% (4) or 15% (6).

Re-formulating the Question

Another defect of the studies summarized above is that they may deal with an inappropriate question. Most appear to have been attempting to provide estimates of the fraction of present-day cancer incidence that is attributable to occupational exposures in the past, to agents that have already been demonstrated to be carcinogenic. However, such a question is of limited interest because the most important consequences of exposures in the recent past will not be manifested until some time in the future. The question that needs to be addressed is "What is the likely contribution of present-day occupational exposures to future cancer incidence?" An answer to this question must be somewhat speculative, because we do not know which of the chemicals in the present-day workplace will be identified sometime in the future as causing cancer. Accordingly, to provide a basis for making appropriate estimates, we will first attempt to estimate the contribution of occupational exposures to known carcinogens in the recent past to present and future cancer incidence. It is not particularly helpful merely to speculate about the possible existence of hazardous chemicals in present-day workplaces.

Asbestos as a Well-Studied Example

The consequences of occupational exposure to asbestos in the United States have only begun to be recognized in the recent past (12-14). It has been estimated* (11) that between 8 and 11 million

* Several authors of this report were responsible for preparing these estimates.

workers have been exposed to asbestos in the U.S. since the beginning of World War II. Of that total, approximately 1.5 to 2.5 million are presently employed. Probably a million have already died, while the remainder--between 5.5 and 7.5 million workers--were formerly employed in environments with significant asbestos exposure, including the survivors among the 4.5 million who worked in shipyards during the 1940's. Of these and other asbestos workers, approximately 4 million are believed to have had heavy exposure to asbestos (11). Epidemiological studies of workers (13-15) have indicated that, of heavily exposed workers who have already died, 20-25 percent have died of lung cancer, 7-10 percent of pleural or peritoneal mesothelioma, and 8-9 percent of gastrointestinal cancers, adding up to a total of 35-44%. These figures may be underestimates of lifetime cancer risks, because most of these workers have not been followed to the end of their life span.

Of the 4 million heavily exposed workers, at least 1.6 million are thus expected to die of the asbestos-related cancers listed above. [In the absence of exposure to asbestos, about 0.35 million (8-9 percent) would have been expected to die of cancers at these sites.] Assuming that the excess risk to the remaining less heavily exposed workers is one-quarter of that to the heavily exposed workers (an assumption suggested by the data in ref. 16), the total number of cancers attributable to asbestos in the less-heavily exposed group would be expected to be in the range 0.4 to 0.7 million, raising the total to 2.0 to 2.3 million. Since most of these cancers will be manifested over a period of 30-35 years, the expected average number

of cancer deaths associated with asbestos per year in that period will be between 58,000 to 75,000.* Such numbers would comprise 13-18% of all cancer deaths expected in the United States in the forseeable future (assuming that total cancer deaths increase to 400,000 to 450,000 per year).

Three features of these estimates deserve emphasis:

1. Although most of the exposure to asbestos has been in the past, most of the predicted effects are expected to be in the future. An estimate of the present-day numbers of cancers attributable to asbestos would undoubtedly be smaller.

2. A large fraction of the asbestos-related cancers are also related to smoking (lung and esophagus) or are in the gastro-intestinal tract (esophagus, stomach, and colon), where cancers are usually assumed to be not occupationally related (1,4,5,6). Hence, if the old one-effect, one-cause approach were used, the occupational origin of most of the asbestos-related cancers would be overlooked and they might be attributed to other or "unknown" factors.

3. Although the frequency of asbestos-related cancers is already substantial and is probably increasing rapidly, it has not yet been detected by examination of gross trends in cancer incidence (or mortality) in the general population. There are several reasons for this:

(a) two of the major types of asbestos-related cancer, pleural and peritoneal mesothelioma, are not classified as such in the national health statistics, but are usually listed as lung cancers or as various abdominal cancers, respectively;

(b) most asbestos-related lung cancers are also smoking-related,

* Selikoff (15) made an estimate of 50,000 per year, exclusive of the added cases that would come among the less heavily exposed group.

so that if one thinks one has the full explanation for the rise in lung cancer incidence in smoking, it is likely that no other causes will be looked for;

(c) any increase in asbestos-related cancers of the stomach and colon would be masked by the other long-term trends in cancer incidence at these sites (down in the stomach, probably up in the colon); these long-term trends are usually attributed to dietary or unknown factors.

Perhaps the most important lesson to be learned from the asbestos story is that a major public health disaster can develop while its early manifestations are lost by being attributed to other factors. This would support the argument that the earlier estimates for industrially related cancers may be deceptively low--having left out such information as the asbestos situation has now brought to our attention.

Comparison of Risks due to Asbestos with those due to Five Other High-Exposure Substances

In Table 2 we have tabulated data on carcinogenic risks associated with exposure to five other substances to which there is large-scale occupational exposure, for comparison with corresponding data on asbestos. The tabulation is similar to that presented in ref. 17, but incorporates more recent data where available, and is limited to the substances and cancer sites for which the best data are available on both exposure and relative risks.

The first three columns in Table 2 list the agent, the affected organs, and the observed risk ratios (R) (from Table 1 in ref. 7). The fourth column lists the age-adjusted incidence (I) of cancer at the sites in question in U.S. males (from data presented in the Third National Cancer Survey, ref. 19). The figures tabulated are the age-adjusted incidences in males over 20 years of age, because most occupational exposure starts at around that age. The fifth column lists the estimated number of workers (N) exposed to the chemical in 1972-74 (from ref. 18, derived from the National Occupational Hazard Survey, ref. 20). The notes to Table 2 give further information about each chemical, including summaries of data from the most definitive studies of each, and references to excess cancers at sites other than those listed in the Table.

The last column in Table 2 lists values of the quantity (R-1)NI. This is the average number of excess cancers that would

be expected to occur in a population of size N, subject to a site-specific risk R times that in the general population. Although these figures are crude projections of the numbers of excess cancers to be expected in the exposed workers, they are unlikely to be precise estimates of future cancer mortality, for several reasons.

Perhaps the most important reason is that they are projections of the numbers of excess cancers in only one cohort of N workers. Because of turnovers in the workforce, the number of exposed workers and ex-workers subject to excess cancers at any one time will be several times larger than N. If, for example, the total number of workers who have ever been exposed to a substance is, say, 5 times the number currently exposed, then the figures in Table 2 would underestimate the potential effects by a factor of 5.

It is primarily for this reason that the data for asbestos in Table 2 underestimate the expected future mortality from asbestos-related cancers by a factor of 4-5. Because the data for the other substances in Table 2 were derived in the same way as those for asbestos, they may likewise underestimate the number of cancers attributable to these substances.

The other major assumption that is necessary before the figures in Table 2 can be used as predictions of future cancer

mortality is that the relative risks R would remain the same as those reported in the published studies throughout the workers' lives, even if exposures ceased. The basis for this assumption is discussed in Appendix A, where both observational and theoretical reasons for assuming constancey of R are put forward. In any case several of the studies from which the figures in Table 2 are derived reported average risks over a substantial fraction of the workers' lives.

Several other factors complicate the interpretation of the figures in Table 2, including the potential consequences of simultaneous or sequential exposure to other carcinogens or modifying factors. One reason why Table 2 may overestimate numbers of tumor cancers is that some of the workers presently exposed may have less exposure than the workers from whom the risk ratios R were originally derived. For these reasons, the figures should not be interpreted as precise estimates of future cancers, but it is reasonable to compare them with the data derived by the same method for asbestosrelated cancers. At the least, the data summarized in Table 2 show that the five other agents together pose hazards similar to or greater than those posed by asbestos. The sum of the best projections (see notes to Table 2) for the five compounds is about 33,000 cancers per year, versus 13,900 for asbestos. In presenting this comparison, it should be emphasized that the former figure includes only the primary sites of action. Inclusion of expected excess cancers at other sites would increase the

estimates substantially.

It should be re-emphasized that many of the cancers considered here as attributable to occupational exposure would simultaneously be attributable to other factors, especially smoking. They are "attributable to" occupational exposure in the sense that most of them would not have occurred in the absence of exposure, so that they could have been prevented by prevention of occupational exposure.

Other Known and Potential Risks

In addition to the five major agents listed in Table 2, a number of other agents and industrial processes are known or suspected to pose carcinogenic risks to exposed workers.

We omitted from Table 2 several agents listed as occupational carcinogens in refs. 7, 8 and 17, because we had difficulty matching data on relative risks to data on the number of workers exposed. These agents include cadmium, coal tar pitch volatiles, hematite, and vinyl chloride. The data we used on the number of workers exposed to carcinogenic petroleum fractions are probably conservative. The IARC (8) has already reviewed 221 agents identified as capable of inducing cancer in experimental animals. Although some occupational exposure is known to occur for most of these chemicals, epidemiological and case studies of their possible association with cancer in humans were lacking or were judged to be "inconclusive." Other carcinogens have been reported in the literature. To date only a very small proportion

of all the chemicals in use have been tested for carcinogenicity.

Table 3 lists a number of occupational groups that have been shown to be at increased risk of cancer at specific sites, without specific causative agents having been identified. Although risks ratios are available in most of these cases, the imprecision of information on the numbers of workers in the jobs concerned prevented us from making estimates about the number of cancers to be anticipated.

In addition to chemical carcinogens, occupational exposure to radiation is known to be a significant cause of cancer in U.S. workers. Groups at risk include radiologists, uranium miners, workers in the nuclear industry, military personnel exposed to radiation from nuclear explosions and to nuclear weapons, aircrews, and persons working at high altitudes. Persons working outdoors such as farm workers and fishermen are subject to increased risks of skin cancer associated with solar radiation. We have not attempted to make numerical estimates of expected cancer incidence in these occupations although many millions of workers are at presumptive risk.

Consequences of Present-Day Exposures

The estimates of potential excess cancer mortality that are listed in Table 2 are projections of the future consequences of past exposures. The estimates of risk ratios listed in Table 2 are derived from studies published between 1947 and 1978, mostly since 1966 (7). The estimated numbers of workers exposed are derived from a survey in 1972-74 (20). The anticipated excess

cancer incidences are those expected to be observed in the next three decades, and could exceed those currently occurring and attributable to the agents in question.

There is evidence that occupational exposure to several of these agents has been reduced since the studies developing the risk estimates were published. Exposure to asbestos, benzene, coke oven emissions and vinyl chloride has been limited (although not eliminated) by recent OSHA regulations.

There is also evidence, however, that not all the major occupational carcinogens have been eliminated. Of the agents in Table 2, there is today widespread exposure to arsenic, chromium, nickel, and many petroleum products. Most of the excess risks referenced in Table 3 remain uncontrolled because the causative agents have not been identified. A number of important occupational groups (such as agricultural field workers) have not been adequately surveyed for excess cancer risks. Only a handful of the 221 chemicals found positive in experimental animals and reviewed by the IARC (8) have been regulated as carcinogens in the U.S. workplace. Among those not regulated are a number of synthetic organic chemicals to which there is widespread occupational exposure, but which have not been in production for long enough periods for excess risks to have been identified by epidemological studies.

For public policy purposes, it would be very desirable to make numerical estimates of the potential consequences of present-day exposure to carcinogens in the workplace. Such estimates

would, however, require numerical data on the extent and intensity of exposure, and on dose-response relationships in experimental animals. If sufficient data were available, prediction of future consequences would require quantitative extrapolation from animal responses to man. In our view, existing methods for such extrapolation leave enough questions open concerning their precision so as to make us unwilling to attempt large scale estimates -- particularly in the absence of exposure data. Hence, we can say nothing firm about the magnitude of future risks attributable to the unquantified present-day exposures.

There is no evidence, however, that these risks are substantially less than the risks resulting from exposures in the recent past. Although several of the most important known carcinogens have been controlled, others have not; many carcinogenic and potentially carcinogenic chemicals are still present in U.S. workplaces; the total volume of synthetic organic chemicals produced in the U.S. continues to increase rapidly. If only one of the thousands of chemicals introduced into commerce in the past 30 years proves to be as hazardous as asbestos, this could suffice to maintain comparable rates of occupationally-related cancer for decades into the future. In our view, any complacency about the future consequences of present-day exposure to uncharacterized chemicals would be unjustified.

Two Alternative Approaches

Other ways can be used to estimate the possible contribution of occupational exposures to human cancer incidence. Although none, to our knowledge, has been used formally and quantitatively, at least two have been used informally to argue that occupationally-related cancers cannot be numerically important.

The first approach is to analyze trends in total cancer incidence (or mortality) in the U.S. population. The argument is made that if occupational factors were important causes of cancer, then total cancer incidence whould be increasing rapidly, reflecting the rapid increase in the number and amount of synthetic organic chemicals produced in recent decades. In fact (the argument runs), the continued increase in cancer incidence and mortality is almost solely due to increases in lung cancer and other smoking-related cancers. If the "smoking -related" cancers are subtracted from the total, the argument is that the overall trend is constant or even slightly decreasing.

There are several fallacies in this argument:

1. Most of the increase in production of synthetic organic chemicals is too recent to be reflected in current cancer statistics.

2. The increase in production of synthetics (some of which are potential carcinogens) in the period 1940-1960 may well have been offset by reductions in the intensity of exposure to other chemicals, resulting from improvements in industrial controls stimulated, in part, by government regulation. Exposure to several major carcinogens has been reduced substantially in recent years. Exposure to other potential carcinogens (such as carbon tetrachloride) was reduced earlier, to reduce other types of toxic

hazard. The predicted consequence of reduction in exposure to "old" carcinogens and increase in exposure to "new" carcinogens is consistent with what is observed: an increase in cancer at some sites and a decrease at others.

3. To subtract all the "smoking-related" cancers from the total is sophistry, because at least two of the sites in question are precisely those in which "occupationally-related" cancers are best recognized. Many of the smoking-related cancers should be simultaneously attributable to occupational factors. On a per-capita basis smoking among adults is declining and this should result in a decline in the smoking-related cancers -- but none of this is factored in when all "smoking-related" cancers are removed from the total. If the smoking-related cancers are not subtracted, total age-adjusted cancer incidence in the U.S. is increasing at more than 1% per annum (37).

4. Not all of the smoking-related cancers, i.e. those in the lung, pancreas, and bladder, are attributable to smoking. Even if a liberal figure is used for attributable risk, the fraction of lung cancer incidence not attributable to smoking is increasing and total cancers possibly industrially related have been increasing more rapidly in the last several years than in the two decades from 1950 to 1970 (38).

5. As pointed out earlier, the major public health impact of asbestos-related cancer is just beginning to be reflected in overall cancer statistics, despite 37 years of heavy exposure. One should hardly expect more recent additions to have shown a great effect already.

A second approach is to compare cancer incidence in men and women. To the extent that exposure to chemical carcinogens occurred in occupations in which most workers are (or were) male, this should be reflected in differences in overall cancer incidence (and trends in incidence) in the two sexes. This argument would tend to support the concept of industrial risk.

The predicted difference is in fact observed: age-adjusted cancer incidence is greater in males than in females at every common site except the gall bladder and thyroid (19). In particular, incidence is much higher in males than in females in the key occupationally related sites: lung, liver, bladder, kidney, hematopoetic and lymphatic system and perhaps stomach and pancreas (19).

Nonetheless, there are some flaws in this argument, too. Not only male workers have substantial exposure to carcinogens. Although male workers doubtless predominate in chemical manufacturing and heavy industry, women have long been employed in large numbers in light industry where there is substantial exposure to certain carcinogens, e.g. the radium dial painters. The fraction of occupationally related cancers in women may increase in future years due to increased employment of women in jobs where they are exposed to carcinogens. Even housewives have greater occupational exposure to some potential carcinogens than typical working men.*

* We regard the home as a workplace, even if it does not fall within the jurisdiction of OSHA.

It would clearly be valuable to make a rigorous comparison between employed and never employed women, but such a study would be difficult to conduct and interpret because of the many confounding variables. In our view, there is nothing in the gross cancer statistics for the U.S. population which is inconsistent with the hypothesis that up to 20-40% of all cancers are (or will be in the next several decades) attributable to occupational factors.

Relation between Occupational and Other Contributing Factors

These estimates do not diminish the importance of other contributing factors to cancer risk such as smoking, diet, and perhaps urban-rural differences. While much of the data on occupational cancer risk considered in this paper does not specifically consider factors such as smoking (except for asbestos) and diet, it is also fair to state that the prevailing body of data linking smoking and diet with cancer risk do not adequately consider the contribution of exposure to occupational carcinogens. This is largely because the available scientific methodologies do not facilitate adequate consideration of all contributing factors in any single study or approach. Until recently most scientists did not take into account the multiple etiologies and the multi-stage nature of cancer. In retrospect, it is likely that cancer risk is a function of multiple interacting factors. Past assessments, unfortunately, generally failed to consider adequately one of the most important, and preventable, risk factor, exposure to carcinogenic agents in the workplace.

Opportunities for Prevention

The estimates of cancer attributable to occupational exposure given here should be viewed as pointing up the opportunities that exist to prevent disease in future generations. The causes of cancer are multiple, with more than one factor contributing to cancer risk. In such a situation, any percentage accounting of contributing causes to cancer well exceeds 100%. To prevent cancer, one must concentrate on causative factors that can be reduced so that we can decrease the burden of disease in future generations. It has been argued that present day asbestos workers are at lower risk than earlier workers. Opportunities to reduce risks and subsequent disease in other occupations are at hand.

Summary and Conclusions

1. The estimates that only 1% to 5% of total cancers in the United States are attributable to occupational factors have not been scientifically documented and have little meaning for estimating even short-term future risks.

2. Most cancers have multiple causes: it is a reductionist error and not in keeping with current theories of cancer causation to attempt to assign each cancer to an exclusive single cause.

3. Because cancer incidence is strongly dependent on age and upon duration of exposure, and because most cancer occur late in life, many industrial epidemiological studies detect only a small fraction of cancers (i.e. those developing early).

4. Past exposure to asbestos is expected to result in up to 2 million excess cancer deaths in the next three decades: this would correspond to roughly 13-18% of the total cancer mortality expected in that period.

5. Reasonable projections of the future consequences of past exposure to established carcinogens suggests that at least five of them may be comparable in their total effects to asbestos.

6. These projections suggest that occupationally related cancers may comprise as much as 20% or more of total cancer mortality in forthcoming decades. Asbestos alone will probably contribute up to 13-18%, and the data in Table 2 suggest at least 10%-20% more. These data do not include effects of radiation, nor effects of a number of other known chemical carcinogens.

7. Although exposure to some of the more important occupational carcinogens has been reduced in recent years, there are still many unregulated carcinogens in the U.S. workplaces; a number of occupations are characterized by excess cancer risks which have not yet been attributed to specific agents.

8. There is no sound reason to assume that the future consequences of present-day exposure to carcinogens in the workplace will be less than those of exposure in the recent past.

9. Patterns and trends in total cancer incidence (and mortality) in the U.S. are consistent with the hypothesis that occupationally-related cancers comprise a substantial and increasing fraction of total cancer incidence.

10. The conclusion that a substantial fraction of cancers in the United States are occupationally related is not inconsistent with conclusions that substantial fraction of cancers are also associated with other factors, such as cigarette smoking and diet.

11. Occupationally-related cancers offer important opportunities for prevention.

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TABLE 1

CHEMICALS OR INDUSTRIAL PROCESSES

ASSOCIATED WITH CANCER INDUCTION IN MAN

(Derived from ref. 8, with addition of data on worker exposure from ref. 19; see also footnotes to Table 3.)

Chemical or Industrial Process	Main Type of Exposure[a]	Target Organs in Man	Main Route of Exposure[b]	Estimated No. of Workers Exposed in U.S.
Aflatoxins	Environmental, occupational[c]	Liver	Oral, inhalation[c]	_____ d
4-Aminobiphenyl	Occupational	Bladder	Inhalation, skin, oral	100
Arsenic compounds	Occupational, medicinal, environmental	Skin, lung, liver[c]	Inhalation, skin, oral	1,500,000 g
Asbestos	Occupational	Lung, pleural cavity, g.i. tract	Inhalation, oral	1,600,000
Auramine (manufacture)	Occupational	Bladder	Inhalation, skin, oral	_____ d
Benzene	Occupational	Hematopoietic system	Inhalation, skin	1,900,000
Benzidine	Occupational	Bladder	Inhalation, skin, oral	2,200
Bis(chloromethyl) ether	Occupational	Lung	Inhalation	_____ d
Cadmium using industries (? cadmium oxide)	Occupational	Prostrate, lung	Inhalation, oral	1,400,000

Chemical or Industrial Process	Main Type of Exposure[a]	Target Organs in Man	Main Route of Exposure[b]	Estimated No. of Workers Exposed in U.S.
Chloramphenicol	Medicinal	Hematopoietic system	Oral, injection	_____ d
Chloromethyl methyl ether	Occupational	Lung	Inhalation	_____ d
Chromium (chromate producing industries)	Occupational	Lung, nasal cavities[c]	Inhalation	1,500,000 (chromium oxides)
Cyclophosphamide	Medicinal	Bladder	Oral, injection	_____ d
Diethylstilbestrol	Medicinal	Uterus, vagina	Oral	_____ d
Haematite mining	Occupational	Lung	Inhalation	19,000
Isopropyl oil	Occupational	Nasal cavity, larynx	Inhalation	_____ d
Melphalan	Medicinal	Hematopoietic system	Oral, injection	_____ d
Mustard gas	Occupational	Lung, larynx	Inhalation	_____ d
2-Naphthylamine	Occupational	Bladder	Inhalation, skin, oral	1,000
Nickel (oxides)	Occupational	Nasal cavity, lung	Inhalation	1,400,000[e]
Chlornaphazine	Medicinal	Bladder	Oral	_____ d
Oxymetholone	Medicinal	Liver	Oral	_____ d
Phenacetin	Medicinal	Kidney	Oral	_____ d

Chemical or Industrial Process	Main Type of Exposure[a]	Target Organs in Man	Main Route of Exposure[b]	Estimated No. of Workers Exposed in U.S.
Phenytoin	Medicinal	Lymphoreticular tissues	Oral, injection	_____ d
Soot, tars and oils	Occupational, environmental	Lung, skin, scrotum	Inhalation, skin	_____ f
Vinyl chloride	Occupational	Liver,[c] brain,[c] lung[c]	Inhalation, skin	2,200,000

[a] The main types of exposure mentioned are those by which the association has been demonstrated.

[b] The main routes of exposure given may not be the only ones by which such effects could occur.

[c] Denotes indicative evidence

[d] Not recorded in the survey: exposure very small in all cases except aflatoxins.

[e] No. of workers exposed to nickel oxide: only about 230 workers exposed to nickel carbonyl

[f] Exposure very large but not characterized numerically

TABLE 2

REPORTED RISKS ASSOCIATED WITH OCCUPATIONAL EXPOSURE: COMPARISON BETWEEN ASBESTOS AND FIVE OTHER HIGH-EXPOSURE SUBSTANCES

Chemical Substance	Affected Organs	Risk Ratio (R)[a]	Age-adjusted Incidence per 100,000 Males $\geq$ 20 yrs (I)[b]	Estimated No. of Workers Currently Exposed (N)[c]	(R-1)NI
Asbestos	Lung, pleural and peritoneal mesothelia	1.5-12	116	1,600,000	900-19,000
Asbestos	Lung, pleural and peritoneal mesothelia	6.6[d]	116	1,600,000	10,400
Asbestos	Esophagus	2.7[d]	9.4	1,600,000	250
Asbestos	Stomach	1.7[d]	26.2	1,600,000	400
Asbestos	Colon/rectum	1.6[d]	85	1,600,000	800
Arsenic	Respiratory tract	3-8	131	1,500,000[g]	3,900-14,000
Benzene	Leukemia	2-5[e]	17.9	2,000,000	350-1400
Chromium	Respiratory tract	5-9	131	1,500,000	7,900-16,000
Nickel (oxides)	Respiratory tract	5-10	131	1,400,000	7,300-16,500
Petroleum fractions (including aromatics)	Lung	3 (2-33)[f]	116	3,900,000[f]	9,100

[a] From ref. 7 unless otherwise stated: see also detailed notes below.
[b] From ref. 18
[c] From ref. 17, derived from ref. 19
[d] From Table 3 in ref. 15
[e] From ref. 21
[f] From ref. 16: see notes below
[g] From ref. 42

NOTES TO TABLE 2

The figures for risk ratios listed in the table are drawn from the tabulation by Cole and Goldman (ref. 7). The notes below provide further data drawn from the principal published references for each substance.

ASBESTOS

Number of workers potentially exposed: About 1,600,000
Risk Ratios: 1.5 - 12 for lung, pleural and peritoneal mesothelia
Projected number of excess cancers per year: 13,900

From the studies of Selikoff (ref. 15) the relative risk for lung cancer among asbestos-insulation workers in the U.S. is about 6.6, which accounts for about 20% of their deaths. A further 7% of cases are due to mesotheliomas which otherwise occur rarely. Applying the 6.6-fold increase in lung cancer to 1.6 million exposed workers yeilds 10,400 excess cases with roughly another one third or 3,500 due to mesothelioma for a total of 13,900 cases per year. Provisional projections for excess cancers in the respiratory tract, based upon the observed relative risks in Selikoff's study (15) are given in Table 2.

ARSENIC

Number of workers potentially exposed: about 1,500,000
Risk Ratios: 3-8 for respiratory tract cancers
Projected number of excess cancers per year: 7,300

In 1969 Lee and Fraumeni (ref. 21) evaluated the mortality experience of 8,047 white male smelter workers exposed to arsenic

trioxide during 1938 to 1963. Smelter workers were found to have a three-fold excess in mortality from all respiratory cancer compared to a statewide population control group. About half of those in the study population were exposed to arsenic less than 10 years. Of those exposed for at least 15 years and followed another 25 years, the relative risk for respiratory cancer was 4.7. If this excess can be applied to the approximately 1,500,000 workers exposed to arsenic, it is projected that about 7,300 excess lung cancers each year may occur. It should be noted that the cancer risk from exposure to arsenic may be influenced by exposures to other occupational chemicals, such as sulfur dioxide.

Exposure to arsenic has also been associated with excess cancers of the skin and liver (7): these sites are not considered here.

BENZENE

Number of workers potentially exposed: about 2,000,000
Risk Ratios: About 5 for leukemia
Projected number of excess cancers per year: 1,400

A study by Infante, Rinsky, Wagoner and Young (ref. 22) examined the mortality experience of workers exposed to benzene from 1940 to 1949. A significant 5-fold excess risk of death from all leukemias was observed compared to controls (7 observed vs. about 1.4 expected). This study represents an understatement of risk since the 25% lost to followup in the study population were regarded as alive in the statistical analysis. These data are consistent with numerous case reports of leukemia deaths

among workers exposed to benzene. Based on these figures and an estimated occupationally-exposed population of about 2 million, it is projected that about 1,400 excess leukemia cases may occur due to benzene exposure on the job.

CHROMIUM (Trioxide and other hexavalent chromium compounds)

Number of workers potentially exposed: about 1,500,000
Risk Ratios: 3-40 for nasal cavity and sinus, lung and larynx
Projected number of excess cancers per year: 7,900

Enterline (36) noted that the overall SMR for respiratory cancer in a group of 1,200 chromate workers, ages 20-64, who were working some time between January 1, 1937 and December 31, 1940 and who were born after 1889 was 942.6. SMRs decreased steadily over the observational period from a high of 2909.1 in the interval from 1941-45 to a low of 474.7 in 1956-60. From the above, it would seem that a reasonable estimate of the risk ratio for all respiratory cancers among workers exposed to chromium would be at least 5 and perhaps as high as 9. Assuming that an overall risk of 5 can be applied to the approximately 1.5 million exposed workers, it is estimated that about 7,900 excess cancer cases might occur each year.

NICKEL (Oxides)

Number of workers potentially exposed: about 1,400,000
Risk ratio: 5-10 for respiratory tract
projected number of excess cancers per year: 7,300

A Norwegian study by Pedersen et al. in 1973 (34) observed an overall excess respiratory cancer increase of 5.6 fold among

nearly 2,000 men exposed to nickel. The highest risk (risk ratio of 14.0) was observed in men first employed before 1930 and followed for at least 40 years. Assuming that an overall risk ratio of about 5 for all respiratory cancers can be applied to the approximately 1,400,000 workers estimated exposed to nickel, it is projected that about 7,300 excess respiratory cancers, excluding nasal cancer, will occur each year. Studies by Doll (35) document the dramatic decrease in risk from respiratory cancer when positive action has been taken to reduce occupational exposure to nickel. Exposure to nickel compounds is also associated with excess cancers of the nasal sinuses (7): these cancers are not considered here.

PETROLEUM PRODUCTS, INCLUDING AROMATIC HYDROCARBONS

Number of workers potentially exposed: about 3,900,000
Risk ratios: 2-33 for lung cancer
Projected number of excess cancers per year: 9,100

The carcinogenic properties of petroleum products, especially polynuclear aromatic hydorcarbons (PNHs) have been well studied. Lung cancer risk ratios in the range of 2 to 33 have been observed for coke oven and gas workers in the U.S., England, and Japan exposed to PHNs which are contained in petroleum products (Doll, Lloyd, Kawai, Kalzumdar, Redmond). Excess lung cancer risk rates have also been observed for roofers in the U.S. (Hammond). Less well appreciated is the fact that many other occupational groups are exposed to aromatic hydrocarbons, including polynuclear aromatics; these groups include mechanics, electricians, and workers in the printing industry. (Menck and Henderson ref.

16). The risk ratios for lung cancer in these groups range from about 2 to 4. The number of workers estimated to be exposed to aromatic hydrocarbons, including polynuclear aromatics, is about 3,900,000. Assuming that an overall lung cancer risk ratio of 3 can be applied to these workers, it is estimated that about 9,100 excess lung cancer deaths each year might occur in this group.

TABLE 3. OCCUPATIONAL GROUPS IN WHICH EXCESS CANCER INCIDENCE HAS BEEN REPORTED WITHOUT IDENTIFICATION OF A SPECIFIC ETIOLOGIC AGENT

Occupational Groups	Cancer Site(s)	Percent Excess Reported	Ref.
Coal Miners	Stomach	40	23
Chemists	Pancreas, lymphomas	64 79	24
Foundry Workers	Lung	50-150	25,26
Textile Workers	Mouth and pharynx	77	27
Printing Pressmen (newspaper)	Mouth and pharynx	125	28
Metal Miners	Lung	200	29
Coke by-product Workers	Large intestine, pancreas	181 312	30
Cadmium Production Workers	Lung, prostate	135 248	31
Rubber Industry			
Processing	Stomach, leukemia	80 140	33
Tire Building	Bladder, Brain	88 90	33
Tire Curing	Lung	61	33
Furniture Workers	Nasal cavity and sinuses	300-400	39
Shoe Workers	Nasal cavity and sinuses, leukemia	700 100	39,40 41
Leather Workers	Bladder	150	7

Note: With the possible exception of the lung cancers and leukemias, there is no overlap between the excess cancers listed in this table and Table 2.

APPENDIX A

ESTIMATION OF LIFETIME RISKS FOLLOWING OCCUPATIONAL EXPOSURE

A major part of the preceding paper concern the prediction of lifetime risk following occupational exposure to carcinogens during all or part of a working life. The estimates were derived assuming that relative risks remain constant for the rest of the lifetime, the estimated values for the relative risks being derived from cohorts with their own particular distributions of age, and both age at, and duration since first exposure. The purpose of this Appendix is to show that the assumption of constancy of relative risk has a reasonable basis. Both relevant epidemiological data and the predictions of mathematical models of carcinogenesis will be considered.

Epidemiological data from four types of exposure are discussed: asbestos, nickel, radiation, and cigarette smoking. The latter two are not primarily occupational exposures, but they provide the two examples best studies with regard to evolution of risk after exposure.

For cigarette smoking, the incidence of lung cancer increases with the daily amount smoked (either linearly or perhaps quadratically) and with the fourth power of duration of smoking, for current smokers. On stopping smoking the incidence does not further increase, but remains approximately constant with age until it approaches that of non-smokers after some 20 years (Doll and Peto 1976). The relative risk therefore falls within five years of stopping smoking, as shown in Figure 1a.

For radiation, leukemia behaves differently from tumors of epithelial origin. Following a single course of radiation treatment for

ankylosing spondylitis (Smith and Doll 1978), the relative risk for leukemia rises rapidly, reaching a peak within 3-5 years, then decreases to become inappreciable some 12-15 years after exposure (Figure 1b). The relative risks for epithelial tumors of heavily exposed organs, however, remain low until 10 years after exposure, then rise and remain on a plateau for the remainder of the observation period (Figure 1c).

Other epidemiological data on risks from irradiation show similar behavior for leukemia (A-bomb survivors) and for breast cancer (A-bomb survivors, women given radiation treatment for tuberculosis or post-partum mastitis).

The two examples just given provide the two extreme possibilities, continually elevated risk following exposure of very limited duration, or a rapid fall in risk following cessation of a long lasting exposure.

Asbestos and nickel provide two examples of occupational exposures where cohorts have been followed over an extended period of time. Asbestos causes lung cancer, cancer of the gastrointestinal tract, and mesotheliomas (Selikoff and Hammond 1978). Among a cohort more than two thirds of whom had been exposed for less than two years (Newhouse and Berry), the incidence of mesotheliomas increased with increasing rapidity until the limit of the observation period, 35 years after first exposure (Figure 1d). Conversion of these incidence figures into corresponding values for relative risk is not helpful due to the rarity of the non-occupationally related disease. However, the absolute risk, as given by the incidence figure, shows no sign of leveling off even thirty years after cessation of external exposure. Extrapolation of the incidence curve to higher age groups

would seem justified, to give an estimate of 8-10% of deaths due to mesothelioma predicted in the group under study (Newhouse and Berry 1976).

For cancer of the lung the data have not been presented in such clear fashion, but all studies indicate an increase in relative risk for the period more than twenty years after start of exposure compared to 10-19 years after start of exposure. Assumption of a constant relative risk would appear to be conservative (Selikoff and Hammond 1978; Peto et al. 1977; Newhouse and Berry 1976; Knox et al. 1968).

For nickel, the main carcinogenic hazard for the cohort from Wales appears to have been removed from the environment around 1930 (Doll, Matthews and Morgan 1977). Nevertheless, there has been no indication that the relative risk for either lung cancer or for cancer of the nasal sinuses has fallen over the decades following the reduction in hazard (Doll et al. 1970,1977) up to the most recently reported follow-up ending in 1971. Similarly in the Norwegian study (Pedersen 1973), the great reduction in expsoure to dust and fumes since 1950 is not reflected in any reduction in relative risk. Interestingly, the values for the relative risk (average over follow-up to 1971 in both cases) for the Welsh cohorts exposed before 1930 and the Norwegian cohort exposed before 1950 were similar, approximately 10-fold.

One would conclude from these two examples of occupational exposure that the epithelial tumors induced behave more like epithelial tumors related to radiation than to those related to cigarette smoking. Exposure to the aromatic amines would seem similar with risk

among the exposed not falling two deceased after removal from the workplace of the known carcinogens, but in this situation the replacements for the carcinogens may themselves have been carcinogenic (Fox and Collier 1976).

The different types of behavior described above can be devised from the widely accepted multi-stage theory of carcinogenesis, where a cancer is assumed to arise from a single cell which then passes through a series of stages, the last of which leads irreversibly to a clinically apparent tumor. With k stages, and with probabilities of transition constant over age, one would predict the age-specific incidence to increase with age to be (k-1) power, as is observed for most epithelial tumors with k = 5 or 6 (Whittemore 1977; Cook, Doll and Fellingham 1969).

Now suppose that an external carcinogen, as in an industrial exposure, begins to operate at time t_1, and then is removed at time t_2. If cancer is a multi-stage process, then the effect on the incidence of the target organ cancer, and on the relative risk, will depend on which stage in the process is primarily effected. If the initial stage is affected then we expect the relative risk at time t ($t>t_2$) to be of the form:

$$R(t) = 1 + c\,[(1 - t_1/t)^{k-1} + (1 - t_2/t)^{k-1}]$$

where c is proportional to the dose. R(t) is shown graphically for various values of t_1 and t_2 in Figure 2a. The approximate constancy of the relative risk over time for a range of values of t_1 and t_2 is apparent, similar to the behavior for epithelial tumors after irradiation, and probably similar to the effects of asbestos and nickel.

If the penultimate stage is affected, the behavior is different, the relative risk at time t ($t>t_2$) being given by $1 + (t_2/t)^{k-1} - (t_1/t)^{k-1}$, i.e. decreasing rapidly after cessation of exposure, as in Figure 2b.

Cigarette smoking related lung cancer gives an example of this type of behavior.

For mesotheliomas, where because of the low spontaneous incidence relative risk calculations are of little value, a multi-stage model (with K = 3) has been successfully fitted to both animal data and data from 35 years of follow-up of a cohort (Newhouse and Berry 1976).

The multi-stage model appears to give a coherent picture of the evolution of risk after exposure during a limited interval which is consistent with available epidemiological data, at least for epithelial tumors which comprise the great majority of occupationally related cancers. These data, taken together with the implication of the model, give support to the assumption on which many of the numerical estimates of the paper are based, and justify extrapolation of relative risk values obtained from industrially exposed cohorts to the remaining lifetime of the cohort.

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LEGENDS FOR FIGURES

1. a. Incidence rate of lung cancer as a percent of rate at time of stopping.

   b. Risk for leukemia following irradiation for ankylosing spondylitis. Left hand vertical axis shows scale for relative risk, right hand vertical axis shows absolute excess number/10^5 population per year.

   c. Risk for tumors of the heavily irradiated sites, following irradiation for ankylosing spondylitis. Vertical axes as in 1b.

   d. Incidence of mesotheliomata, expressed as cumulative number observed, in years since first exposure to asbestos. Expected incidence obtained from a Weibull model with

   $$\text{Risk} = c\,(t-w)^k$$

   where c, w and k are constant (as given in the figure) and t the time since first exposure.

2. Evaluation of risk after exposure of limited duration as predicted by a multi-stage model of carcinogenesis.

   a. First stage effected by the exposure.
   b. Penultimate stage effected by the exposure.

FIGURE 1A

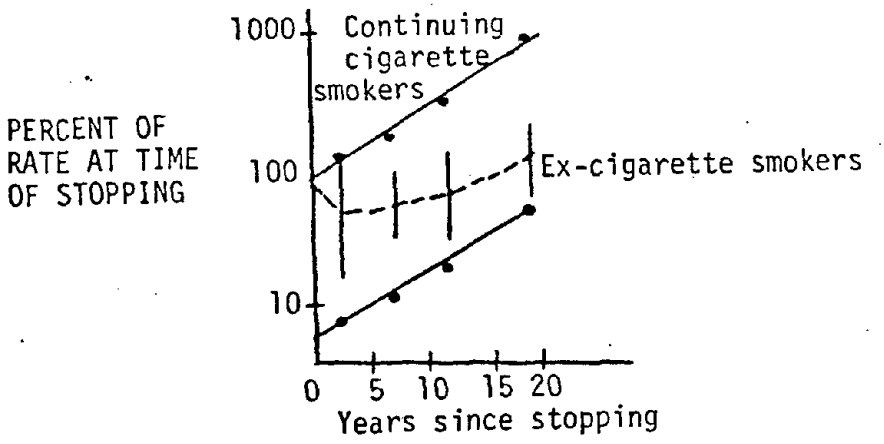


FIGURE 1B

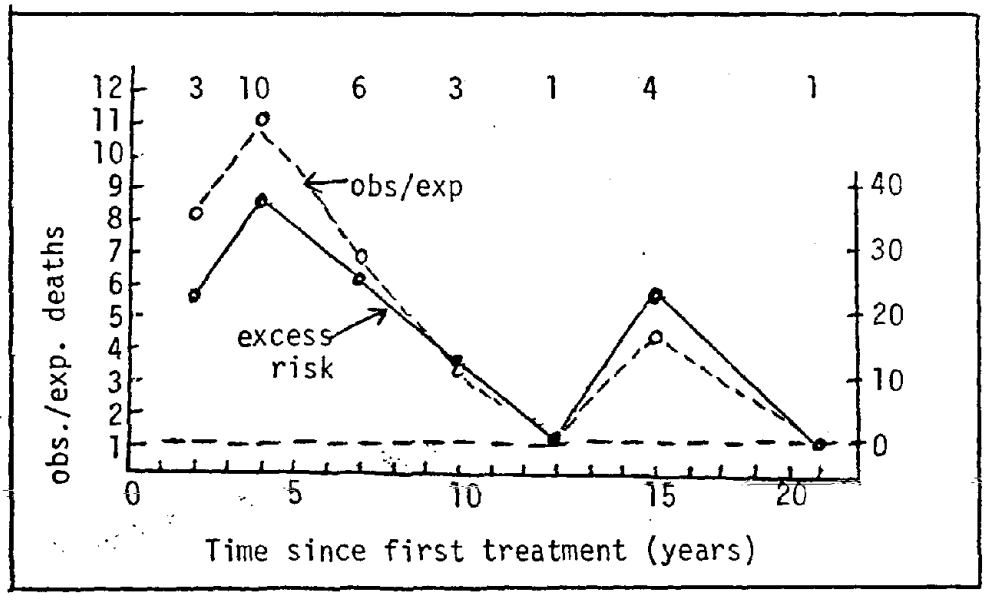


FIGURE 1C

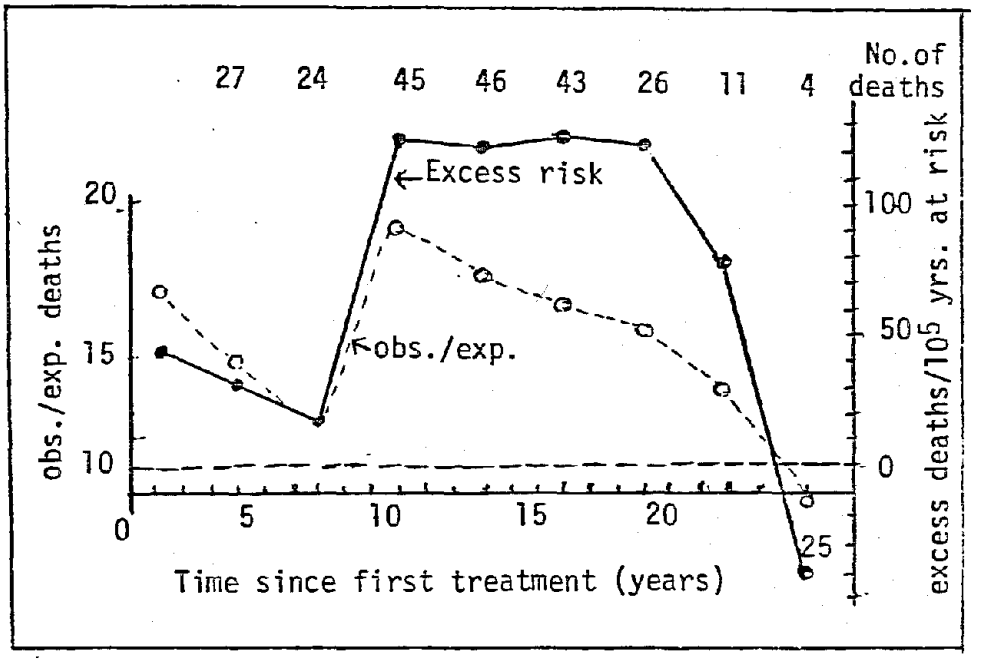


FIGURE 1D

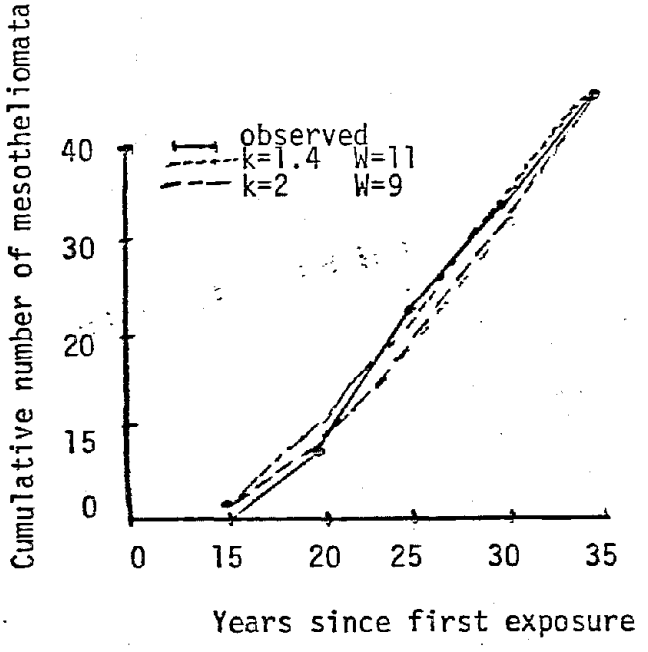
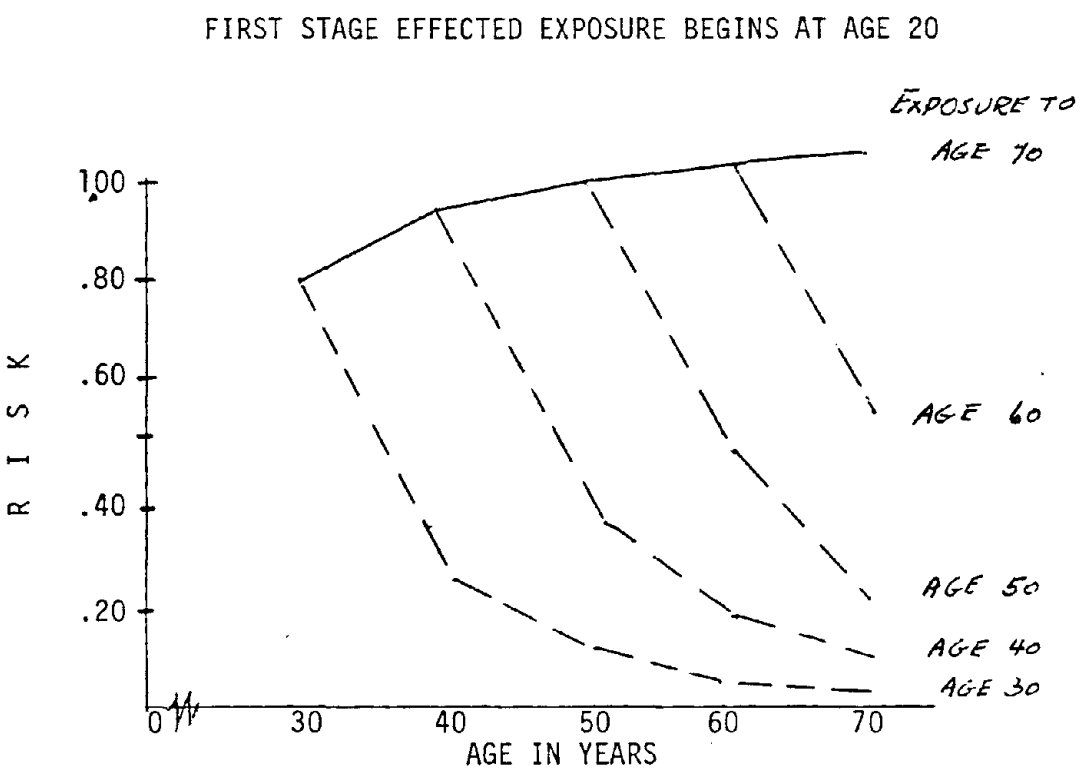


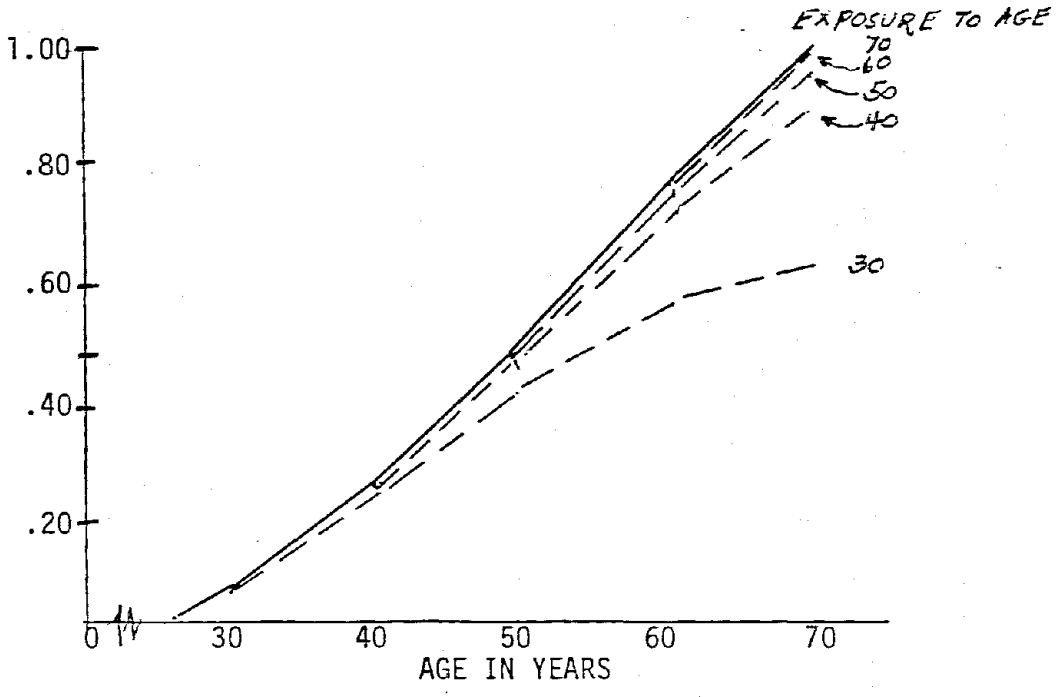
FIGURE 2A



Evolution of Relative Risk After Limited Exposure, Expressed as Percent of Relative Risk Associated with Exposure Through Age 70

FIGURE 2B

PENULTIMATE STAGE EFFECTED EXPOSURE BEGINS AT AGE 20



Evolution of Risk After Limited Duration Exposure,
Expressed as Percent of Risk Associated with Exposure
Through Age 70