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AMERICAN INDUSTRIAL HEALTH COUNCIL

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November 1978

At the suggestion of the Steering Committee of
the American Industrial Health Council, the following documents
are enclosed for your information:

- 1) Reply to the "Estimates of the Fraction of Cancer in the United States Attributable to Occupational Factors" (October 23, 1978)
- 2) "Estimates of the Fraction of Cancer in the United States Related to Occupational Factors" prepared by the National Cancer Institute, National Institute of Environmental Health Sciences, National Institute for Occupational Safety and Health (September 15, 1978)
- 3) Draft Summary of "Estimates of the Fraction of Cancer Incidence in the United States Attributable to Occupational Factors" prepared by the National Cancer Institute and National Institute of Environmental Health Sciences (September 11, 1978).

AP00008850



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A Reply to:

"Estimates of the Fraction of Cancer in the
United States Attributable to Occupational
Factors" (September 15, 1978)

October 23, 1978

AP00008851

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Introduction

The American Industrial Health Council (AIHC) has reviewed the recently released government paper "Estimates of the Fraction of Cancer in the United States Related to Occupational Factors" which was filed in the OSHA post hearing record on September 15, 1978 (referred to hereafter as "Estimates Paper"). This document predicts a massive increase in estimated cancer incidence and mortality due to occupational exposures. While recognizing that occupationally-related cancers do occur and that this incidence must be reduced, AIHC believes scientific evidence does not support the contention that the magnitude of the problem even approaches the projections made in the Estimates Paper.

The following analysis by the AIHC presents documented examples to demonstrate the questionable logic used in the Estimates Paper. In this Reply, AIHC discusses the methodology used in the Estimates Paper and examines specific contentions of the Estimates Paper for asbestos, arsenic, chromium and polynuclear aromatic hydrocarbons plus the basic epidemiology concepts used in the Paper. A complete detailed discussion of the Estimates Paper is presented in Appendices to this Reply. To make this analysis, it was necessary to try to reconstruct the statistical manipulations performed through review of the Paper's source references. This analysis revealed selective use of data, which was often outdated and of questionable scientific validity.

In preparing the Estimates Paper, asbestos has been chosen as the keystone for its argument. Asbestos is an attractive example for a document such as this; it is universally accepted as a carcinogen; many studies exist; excess mortality has been documented; and there is a high level of public and political awareness of its health hazards. Many of these same characteristics make it an unusual carcinogen. The document does not mention, for instance, that no other industrial carcinogen is suspected of so many deaths, nor that such other carcinogens are unlikely to exist currently without our knowledge. Data available from both the Surveillance Epidemiology and End Results Program (SEER) of the National Cancer Institute and the Third National Cancer Survey (TNCS) belie the projections of an asbestos epidemic contained in the Estimates Paper. If the Paper is correct, our country should at present be experiencing a marked increase of mesothelioma (the marker disease for asbestos), and it is not. As described more fully in the attached Appendix A, using the methodology set out in the Estimates Paper itself, one would project a present-day mesothelioma incidence of at least 5,000-9,000 annually (using some very conservative assumptions) and possibly as high as 10,000 or more. In fact, SEER data indicate that the national annual incidence is less than 1,000.

In predicting enormous future mortality from asbestos, the Estimates Paper (a) overestimates the number of people in the previously heavily exposed WW II cohort still alive since mortality has been occurring for many years due to many causes; (b) dis-

regards the fact that asbestos exposure has been declining by both number of workers and by degree of exposure in recent years; and (c) ignores any changes in smoking habits, especially among asbestos workers, that should have important effects on reducing asbestos mortality. Although specific calculations for the asbestos case study are presented in Appendix A, some of the faulty logic followed in this example has been noted here since the Estimates Paper advocates extending these principles to other carcinogens.

Significant errors in estimation of cancers attributable to occupational causes were made for many of the other hazards considered. In the case of arsenic, populations at risk were exaggerated by ignoring significant changes in industrial applications. The Estimates Paper failed to mention the fact that certain major industries no longer use arsenic in their processes. This matter had been addressed only recently by OSHA in its inorganic arsenic rulemaking. OSHA's own conclusion on this issue does not support the Estimates Paper's inflated number of workers at risk from exposure to arsenic.

The Estimates Paper indicates that 1.5 million workers are currently exposed to some form of chromium compounds, with the clear implication that all of these workers are at significant risk. The reference cited in the Paper refers to workers whose exposure may be only inferred or potential rather than actual. Furthermore, among the 1.5 million exposed workers, NIOSH indicates a sizeable number of these persons are exposed

to chromium compounds not considered to be carcinogenic. Here again, the Estimates Paper appears to be less than scientifically objective.

To estimate the lung cancers attributable to Polynuclear Aromatic Hydrocarbons (PNA) exposure, the Estimates Paper applies the relative risk of various cohorts of coke oven and gas workers to a wide variety of workers potentially exposed to PNA's in other industries. The exposures in other industries, however, are very different from the exposures of coke oven and gas workers. Extrapolation between industries therefore is inappropriate and misleading.

It is AIHC's position that whenever a confirmed or highly probable cause of cancer is found in the workplace, there is good and sufficient reason to take prompt and stringent protective action. The scientific evaluation of the risks involved, however, must be thorough and sound. When estimates such as those in the Estimates Paper are made on the basis of unsound methods, erroneous data and an unscientific analysis, AIHC feels it is necessary to try to put the record straight. That is the purpose of this Reply.

CRITICAL REVIEW OF METHODS USED IN ESTIMATES PAPER
TO PREDICT CANCER MORTALITY DUE TO OCCUPATION

The Estimates Paper purports to predict the number of deaths from cancer likely to occur in the future, due to past and present industrial exposure to carcinogens. The prediction is based on the following formulation:

Annual Excess Deaths Due To Occupation =

$$(\text{Risk Ratio} - 1) \times \frac{\text{Age-Standardised Cause-Specific Incidence Rate} \times \text{Exposed Population}}$$

Obviously, any errors in determining risk ratios, representative rates, or of population at risk will result in a multiplication of those errors.

In fact, serious errors have been made in determining all three multipliers, and these errors have yielded exaggerated estimates of excess mortality due to occupational exposures. Specifically, the estimates have the following major problems:

- . Risk ratios inapplicable to recent workplace conditions were used.
- . Inflated estimates were made of the exposed population. 1972 estimates of numbers of potentially exposed workers were taken as the number of workers currently and actually exposed.
- . The concept of attributable risk was confused with associated risk, ignoring the risk of such cancers in unexposed workers and ignoring

other risk factors.

- Age-standardized rates based on specific age-sex distributions were applied to large cohorts whose age and sex distribution is entirely unknown.
- Incidence rates were used as equivalent to mortality without adjustment for survival or competing causes of death.

Use of Inapplicable Risk Ratios

In the appendix of this Reply, we have examined in more detail the problems with specific estimates relating to risks from particular substances. In the Estimates Paper, risk ratios generally are taken from studies of workers exposed in the 1920's - 1950's. Workplace conditions for known carcinogens, and for a great many other chemicals also, have, however, improved considerably since then. Applying a risk factor associated with heavy exposure to workers no longer subject to heavy exposure must grossly overestimate the risk to the worker. In his asbestos studies, Selikoff acknowledges that it is probably reasonable to conclude that "cancer risk varies directly with exposure."^{1/} Exposures have been much lower in recent years yet no adjustment is made for this.

^{1/} Selikoff, I. J. and Hammond, E. C. "Multiple Risk Factors in Environmental Cancer", Persons at High Risk of Cancer, at 467-483, 1975.

The Estimates Paper's treatment of arsenic is a good illustration of this point. The risk ratios used to assess the risk of exposure to arsenic by the Estimates Paper is 4.7^{1/}. This risk ratio, derived from the Lee and Fraumeni study,^{1/} was found by the authors in only one cohort of persons who worked during the early process days. In a second cohort in the same study, exposures of at least 15 years duration, but later in time, yielded a risk ratio of 3.7; 10-14 year exposures gave a risk ratio of 2.3. All of these risk ratios, however, are based on conditions considerably worse than those that have existed for the past 15 years. The authors acknowledge a "gradient in proportion to the degree of exposure." However, the Estimates Paper utilizes the highest figure ever reported, whereas even the lower reported risk ratios are undoubtedly too high to apply to workers exposed within the last 15 years.

The risk ratio of 5 used in the chromium estimate is similarly inappropriate because the studies conducted were largely based on data from the 1930's and 1940's from old chromate-producing plants. In a recent report (1978) of chrome pigment workers by Davies,^{2/} no excess risk was seen among persons with "low exposures" in two factories (exposure dates 1932-1954 and 1948-1967). Nor was excess risk found over all exposure strata in a cohort of workers employed during 1955-1967.

^{1/} Reference 21-The Estimates Paper.

^{2/} Davies, J. M. "Lung-Cancer Mortality of Workers Making Chrome Pigments", The Lancet, at 384, 1978.

The risk ratio of 6.2 used in the nickel category is also exaggerated. A 1977 study by Doll,^{1/} a reassessment of the study referenced in the Estimates Paper, states that the six-fold excess found was confined to persons exposed before 1930 and that no significant excess of lung or nasal cancer was seen among persons first exposed during the period 1930-1944, after process changes had been implemented.

Use of Inappropriate Estimates of the Exposed Population

The exposed population figures used in the Estimates Paper (with the exception of asbestos and arsenic) are based on the National Occupational Hazard Survey (NOHS) document published in 1977. This survey did not measure levels of exposure and, in fact, included actual, potential, or inferred exposures as well as part-time exposures. In the case of chromium, for example, only 16% of the 1.5 million workers considered as potentially exposed by NOHS were full-time workers. (Definition of full-time was at least 4 hours per day.) In addition, not all of the 1.5 million workers in the chromium oxides industry were potentially exposed to hexavalent chromium compounds, the only chromium compounds which have been found to be carcinogenic.

The same problem occurs with the nickel estimates.

^{1/} Doll, R., Mathews, J. D., Morgan, L. G., "Cancers of the Lung and Nasal Sinuses in Nickel Workers: A Reassessment of the Period of Risk", Brit. J. of Industr. Med. 1977 34:102-105.

The risks refer to persons engaged in nickel refining (and as stated earlier, they pertain to a time when exposures were much heavier). The estimated number of workers currently exposed as reported in the Estimates Paper, however, includes many jobs in addition to those involving nickel refining.

With respect to asbestos, the numbers are apparently a combination of an estimate of 4.5 million WW II shipyard workers by Dr. Selikoff and an estimate of 3.5-6.5 million exposed workers based on some unidentified factor of work force turnover applied to NOHS data. All attempts to ascertain documentation for the figures contained in the Estimates Paper have proven fruitless.

With respect to arsenic, the exposed population figure of 1.5 million is based on 1964 data cited in the 1975 NIOSH Criteria Document. OSHA's own Inflationary Impact Statement on Inorganic Arsenic rejected that outdated number. OSHA concluded that of an exposed population of 660,000 a "large number" work in areas where exposures are "very low or non-existent."

Faulty Use of Incidence Rates to Estimate Mortality

Table 2 of the Estimates Paper is used to predict future cancer mortality. In using incidence rates instead of mortality rates, an incorrect assumption is made: namely, that all persons who are diagnosed with cancer subsequently die with cancer as the underlying cause. This clearly is not the case. Many cancer patients die eventually of other causes.

In contrast to the incidence rates given in Table 2, 1970 mortality rates for males over age 20 for neoplasms are given below.

	Age-Adjusted Incidence, 1969-70 per 100,000 Males, 20 years+ */	Mortality Rate, Males, 1970 20 years+ **/	‡ Excess Incidence Over Mortality
Lung	116	88	32
Esophagus	9.4	7	34
Stomach	26.2	16	64
Colon/rectum	85	37	130
Respiratory Tract	131	94	40
Leukemia	17.9	12	49

*/ Source: Third National Cancer Survey.

**/ Source: Vital Statistics of the United States 1970-Vol II-Mortality, at 1-197, 6-17.

It can be seen that incidence rates are considerably higher than mortality rates. While cancer incidence itself is tragic, using the higher incidence rates as though equivalent to mortality rates is inappropriate and greatly compounds error.

In addition, the Estimates Paper ignores important temporal changes in mortality rates. For example, stomach cancer death rates have been steadily decreasing, lung cancer deaths have been steadily increasing. Such changes, along with other factors, make it impossible to project a decade, or several decades ahead.

The use of mortality rates or the use of incidence rates with adjustment for survival and competing causes of mortality would have been a more accurate way to estimate deaths. Fur-

ther, age and sex distribution of exposed cohorts were never considered in the Estimates Paper, thereby rendering invalid the use of age-standardized rates to predict mortality in the totally unspecified cohort.

Attributable Risk Confused With Associated Risk

Presumably, a key question is "what fraction of deaths could be prevented by reduction of industrial exposure?" To follow the logic of the Estimates Paper, Worker 1, in a group of 10 men, who previously worked in asbestos application and uranium mining and smoked, would have his death attributed to each of several factors. Suppose each of the other nine men in the group had known work histories as outlined in the table below. All died of lung cancer.

Worker	Smoker	Asbestos	Uranium
1	+	+	+
2		+	
3	+		+
4	+	+	
5			
6	+	+	+
7			
8	+	+	
9	+		
10			

Deaths attributable to smoking	6
Deaths attributable to asbestos	5
Deaths attributable to uranium	<u>3</u>

Total deaths 14

If we accept the Estimates Paper logic, we would then conclude that smoking accounted for 60% of deaths, asbestos for 50%, and

uranium for 30%. We now have "attributed" 140% of deaths and have not yet taken into account genetic susceptibility, diet, or exposure to any other carcinogens.

Thus, under the methodology of the Estimates Paper, a double or triple accounting for each death will occur because a person is tallied as dying more than once if he is potentially exposed, for instance, to both asbestos and uranium. The error of double or triple accounting is magnified by use of NOHS data because a high proportion of workers listed as exposed are only part-time or only inferentially or potentially exposed. In fact, the NOHS estimated 4.38 billion potential exposures among 38.2 million workers. This gives an average of 115 potential exposures per worker (including a sizeable number of clerical and other office workers). Clearly, one cannot assume each death is attributable to each of 115 different exposures. The survey data contained in the NOHS report were not meant to be used in the manner presented in the Estimates Paper.

Summary

AIHC analysis demonstrates that the Estimates Paper, in the haste to complete and release the document, has ignored basic principles of sound epidemiological and biostatistical practice. The Estimates Paper through such practices has come to unscientific and highly speculative conclusions. By selecting high risk ratios applicable to a small group of highly exposed workers, by inflating estimates of workers actually exposed, by

confusing incidence with mortality, by neglecting age and sex distribution of worker cohorts and by confusing attributable risk with statistical association, the Estimates Paper arrives at a speculative conclusion concerning the probabilities of an imminent cancer epidemic due to occupational causes. This conclusion cannot be supported by national cancer statistics of the National Cancer Institute itself.

APPENDICES

Comments On Estimates Paper
With Regard To Asbestos

Summary

An analysis of the Estimates Paper regarding the incidence of lung cancer related to exposure to asbestos shows that the projected increase is of an order of magnitude greater than can be supported by the data. Using data from the National Cancer Institute's SEER Program (Surveillance, Epidemiology and End Results) for the incidence of mesothelioma (a marker tumor for asbestos related lung cancer) approximately 950 cases occur annually in the U.S. The Estimates Paper would predict as a minimum 5,000-9,000 deaths annually from mesothelioma in the World War II shipyard workers alone. This estimate is far afield from current experience and data, underscoring the logical and methodological flaws in the Estimates Paper. Both the risk factors utilized and the population assumed to be at risk are greatly exaggerated.

Testing The Logic of the Estimates
Paper Against the Available Data

To illustrate the unscientific approach used to obtain the projections in the Estimates Paper, the treatment of asbestos, the "well-studied example", is worthy of some attention.

Mesothelioma, a rare tumor in the general population, is commonly found in heavily-exposed asbestos groups. Thus, it is known as a marker or identifier tumor for cohorts at increased

risk because of heavy exposure to asbestos. ^{1/}

Following the Logic of the Estimates Paper

As a check against the accuracy of the predictions in the Estimates Paper, it may be useful to estimate how many marker mesotheliomas would have been predicted for the U.S. in 1976, using the reasoning and figures in the Estimates Paper which states:

"It has been estimated that between 8 and 11 million workers have been exposed to asbestos in the U.S. since the beginning of World War II. . . . 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." (Estimates Paper at 8-9.)

Continuing with our testing of the logic of the Estimates Paper, let us consider the 4.5 million WW II shipyard workers and suppose the probable million who have already died came entirely from that group, leaving an estimated 3.5 million WW II shipyard workers alive in 1978. This is a very conservative allocation of the "probable million dead," since of the 7-10 million exposed since the beginning of WW II and still alive in 1978 (8 to 11 million, minus one million dead, according to the Estimates Paper)

^{1/} See, e.g., Blot et al, "Lung Cancer After Employment in the Shipyards During World War II," The New England Journal of Medicine, September 21, 1978, at 620-623. Hoover and Fraumeni, co-authors of the article, are also contributors to the Estimates Paper.

we have allocated all deaths to the group with the earliest exposure, thus making it more difficult to find current "asbestos-deaths".

How many of the 4 million who are "believed to have had heavy exposure to asbestos" should be allocated to the 3.5 million surviving WW II shipyard workers? Since the document estimated 7 to 10 million surviving workers have been exposed to asbestos since the beginning of WW II, it follows that 4/10 to 4/7 of surviving workers have had "heavy exposure." Since much of the "heavy exposure" took place during WW II, a conservative allocation (conservative again in the sense of making it more difficult to find current "asbestos-deaths") would assign heavy exposure to only 4/10 to 4/7 of the already conservative 3.5 million. Thus, we have the following table:

Table A-1

Conservative Allocation of Surviving WW II Shipyard Workers to Heavily Exposed Category

<u>Range for Total Exposed and Alive 1978</u>	<u>Surviving WW II Shipyard Workers</u>			
	<u>Total Heavily- Exposed</u>	<u>Heavily- Exposed</u>	<u>Less Heavily- Exposed</u>	<u>Total</u>
7,000,000	4,000,000	2,000,000	1,500,000	3,500,000
10,000,000	4,000,000	1,400,000	2,100,000	3,500,000

Therefore, a conservatively low estimate of heavily-exposed surviving WW II shipyard workers would be between 1.4 and 2.0 million. Virtually all of these WW II workers would have been in their mid-fifties or older by 1976.

According to figures published by the U.S. Bureau of the Census (Statistical Abstract of the United States: 1949),

approximately one in three workers in the civilian labor force during WW II was female. To allow for the fact that age-specific mortality rates are higher for males than females, the female proportion in the surviving WW II shipyard work force will be increased from an initial one-third to 40%.^{1/} Using the figures published by the National Center for Health Statistics ("Vital Statistics Report" Advance Report, Final Mortality Statistics, 1976, DHEW Publication No. (PHS) 78-1120, Vol. 26, No. 12, Supplement (2), March 30, 1978) we see the following age and sex specific death rates:

Table A-2

White Age-Sex-Specific Death Rates, 1976

<u>1976 Death Rates per 1000 Population</u>		
<u>Age Group</u>	<u>Males</u>	<u>Females</u>
55-64	19.2	9.2
65+	67.1	45.8

In 1976, in the 55 and over age groups, slightly over 50% of the males were 65 and over, while over 56% of the females were 65 and over. Therefore, we allocate 50% of the surviving

^{1/} If one were to assume, contrary to this assumption, that fewer women and more men were exposed, one would expect, because of the differences between the sexes in life expectancy and smoking patterns, a shorter-lived cohort with a greater number of deaths in 1976.

... WW II males to each of the two age groups in Table A-2, and 45%
 ... and 55% to the 55-64 and 65+ female age groups, respectively. The
 following calculations can now be made:

Table A-3

Deaths from WWII Shipyard Workers - 1976
White U.S. Age-Sex Specific Rates

Sex/Age Group	Alive at beginning of 1976		Deaths in 1976		
	55-64	65+	55-64	65+	Total
Males	1,050,000	1,050,000	20,160	70,455	90,615
Female	630,000	770,000	5,985	35,266	41,251
Total	1,680,000	1,820,000	26,145	105,721	131,866

For example, if 60% of the surviving WW II shipyard workers are males, and 50% of those are 65+, we get

$$3,500,000 \times .6 \times .5 = 1,050,000$$

in the 65+ age group at the beginning of 1976. (Recall that to be conservative we have not allowed any deaths in 1977.) Applying the age-sex specific death rate of 67.1 per thousand from Table A-2, we get

$$1,050 \times 67.1 = 70,455 \text{ deaths.}$$

How many mesothelioma deaths should there have been, if the conjectures in the Estimates Paper apply? According to the references cited in the Estimates Paper (e.g., (15) and Newhouse and Berry in Appendix A) the latency period is long enough for the "7-10 percent" of deaths to be due to pleural or peritoneal mesotheliomas. Recall from Table A-1 the conservative allocation of past heavy asbestos exposure to the surviving WW II shipyard

cohort. If 2,000,000 were heavily exposed (derived from the assumption of 7,800,000 surviving in 1978), it follows that of the 131,866 deaths, 4/7 will have been from the heavily-exposed group (since 4/7 of the surviving 3,500,000, or 2,000,000 were heavily exposed). Thus at least 7% of the $((4/7) \times 131,866 = 75,352)$ deaths among the heavily-exposed group $(.07 \times 75,352 = 5,275)$ will have been due to mesothelioma. The document assumed that:

"the excess risk to the remaining less heavily exposed workers is one-quarter of that to the heavily exposed workers."

Applying the 1/4 excess risk, we get

$(3/7) \times 131,866 \times (.07) \times (1/4) = 989$ mesothelioma deaths among the less heavily exposed group. Therefore, there should have been at least 6,264 mesothelioma deaths in 1976 from the WW II shipyard cohort. Analogous calculations can be made:

Table A-4

1976 Mesothelioma Deaths Among WW II Shipyard Workers

If Total Exposed and Alive is:	Percentage* Mesothelioma Deaths Among All Deaths	
	<u>7%</u>	<u>10%</u>
7,000,000	6,264	8,949
10,000,000	5,077	7,253

* 1/4 for the less heavily exposed subcohort.

Using the figures in the Estimates Paper, thus far we have

- conservatively allocated the survivors to the cohort of WW II shipyard workers,
- conservatively allocated the heavy exposures to the WW II shipyard cohort,

- dealt only with the WW II shipyard cohort,
- considered white age-sex adjusted death rates with no adjustment for increased risk,

and we arrived at a lower bound of 5,000 to 6,000 1976 mesothelioma deaths. If in fact the mortality experience of the cohorts cited in the Estimates Paper is applicable to the surviving WW II shipyard workers, the death rates should be increased by at least 40%, increasing the lower bound to between 7,000 and 8,400.

The Available Data

The following table contains mesothelioma incidence from the SEER program, obtained from NCI:

Table A-6

Incidence of Mesothelioma for all
Sexes and Races, all sites */

SEER Areas	Total	Years			
		1973	1974	1975	1976
Connecticut	52	9	13	16	14
New Orleans	12	**	1	7	4
Atlanta	2	**	**	**	2
Detroit	63	10	22	14	17
Iowa	43	10	15	11	7
Hawaii	6	1	1	4	0
New Mexico	21	5	5	7	4
San Francisco	95	26	22	20	27
Seattle	41	**	11	15	15
Utah	17	2	4	6	5
Total	352	63	94	100	95

* Unspecified mesothelioma lesions were not classified with malignancies in the Third National Cancer Survey and during the early part of the SEER program. Beginning with the use of the 1976 SEER Code Manual (sometime in 1976 or 1977) unspecified lesions were coded with malignancies.

** Not in the SEER program in that year.

The SEER population represent about 10% of the U.S. population. Disregarding the fact that the SEER population should have an unusually large number of cases (if the projections of the Estimates Paper are true) since five of the areas have a significant ship building industry, these data would indicate a national incidence of about 950 cases of mesothelioma for 1976. Therefore, if there should be at least 7,000 to 8,400 deaths from the WW II cohort alone, the Estimates Paper lower bound for the estimate is at least an order of magnitude too high.^{1/}

Conclusions

Thus far we have dealt only with a conservative lower bound for mesothelioma using only the estimated survivors from the WW II shipyard cohort. If the large numbers of "heavily-exposed" non-shipyard workers are considered, a substantial number should have been exposed during and immediately following WW II

^{1/} Any suggestion that incomplete diagnostic ascertainment would account for at least an order of magnitude is unsupported. The article referred to earlier in this document, co-authored by two of the contributors to the Estimates Paper, rejected this conclusion by noting that: "the failure to see greater numbers of this rare tumor among coastal residents raises the possibility of shipyard hazards in addition to asbestos." To the contrary, there are data that suggest that asbestos awareness leads to an over-reporting of mesothelioma. See McDonald and McDonald, Preventive Medicine, Vol. 6, at 426-446 (1977) (reporting on a mesothelioma survey of pathologists in Canada, the authors found that only 37% of the reported cases in Quebec were accepted by the Mesothelioma Panel of the Canadian Tumor Reference Centre, compared with 60% for the rest of Canada.)

if one accepts the logic set out in the Estimates Paper. Since the probable dead have already been taken into account, all of the non-shipyard workers would have been at risk in 1976 yielding a lower bound for incidence easily exceeding 10,000.

These estimates are obviously unsupportable speculation. Standard life table considerations reveal that far in excess of 1,000,000 deaths would have occurred by 1978 in any civilian worker cohort of 4.5 million from WW II. If the WW II shipyard workers had experienced the increased risk of the heavily-exposed cohorts cited in the document, the WW II shipyard cohort would be almost extinct by 1978. If that were the case, the projections of the next 30-35 years are obviously incorrect.

Looking at the reasoning in the Estimates Paper from another point of view, if the WW II shipyard workers had been at the high risks attributed to them in the document, the marker tumor, mesothelioma, should have shown up in the Third National Cancer Survey in epidemic proportions. Since it hasn't shown up, there is only one conclusion; the Estimates Paper has ignored the spectrum of exposures to asbestos, which, when considered with established dose-response, readily shows that the speculations are at least an order of magnitude too high.

Additionally, there are several important recent studies not discussed in the Estimates Paper. While mortality data on shipyard workers are limited, two recent NIOSH technical reports on the mortality experience of the AFL-CIO United Brotherhood of Carpenters and Joiners of America 1969-1970 (HEW, NIOSH publication 74-

152) both reported:

"Ship carpenters locals have an SMR pattern for total mortality and cancer like the construction worker locals. No remarkable increase in any cancer type is seen."

(The reports did note a slight increase in malignant neoplasms of the pleura - ICD 163.0, an excess of 7.2 deaths over expected, out of 32,707 total deaths. It was attributed to past asbestos exposures by the authors.)

APPENDIX B

Comments on Estimates Paper With Respect to NOHS Data .

Summary

The NOHS survey was inappropriately used by the Estimates Paper authors as a measure of the actual number of workers currently exposed to specific hazards. This survey in fact was only an estimate of the number of workers potentially exposed. Indeed, the authors of the NOHS report specifically "precluded determining relative risk to a given potential hazard."

Introduction

The National Occupational Hazard Survey was a two year study by the National Institute of Occupational Safety and Health intended "to describe the health and safety conditions in the American work environment and, more specifically, to determine the extent of worker exposure to chemical and physical agents." ^{1/}

Purpose, Limitations and Uses

In describing the study, the National Institute of Occupational Safety and Health states that the National Occupational Hazards Survey was "designed to obtain an instantaneous profile for use as a national health hazard information base [and] was to answer such questions as: What occupational groups

^{1/} Preface, by Marcus M. Key, M.D., Director, National Institute of Occupational Safety and Health, NOHS, Volume I, Survey Manual, May 1974.

are exposed to what types of potential health hazards in the United States? in what types of industries can these hazards be found? what types of controls are used to prevent harmful exposure? and to what hazards are the most people exposed?"^{1/} NIOSH indicated that "the National Occupational Hazard Survey [was] aimed at recording specific worker exposures to specific potential health hazards rather than at evaluating severity,...[that it] addressed merely whether a substance was being used,...[and that] this objective approach precluded determining relative risk to a given potential hazard."^{2/}

A statistically selected sampling of the U.S. business establishment (outside of the agricultural area) was developed by the Bureau of Labor Statistics.^{3/} Fifty-two hundred different business facilities, both large and small, were selected. Engineers who had taken a nine-week training course in fundamental industrial hygiene and in field data gathering were selected as a field staff.^{4/} This is in contrast with the National Surveillance Network established by NIOSH which used states' industrial hygienists as evaluators.^{5/} The survey was begun in February, 1972 and scheduled to be completed by June

^{1/} Ibid.

^{2/} Ibid., page 2-3 of introduction.

^{3/} Ibid., page 2-3 of introduction.

^{4/} Ibid, page 3 of introduction.

^{5/} Ibid, page 1-2 of introduction.

of 1974.^{1/} The authors of the report, in discussing the anticipated use of NOHS, indicate many of the limitations of the study and urge that reviewers "must not overlook its limitations. The survey's broad scope and narrow time span have precluded universal application of its results to the problem of occupational health. Though it comprises virtually all industry and employment in the U.S., the survey will not provide precise answers to every hazard query, nor will it stand as a definitive study. It will, however, reveal general occupational environment statistics which should be instrumental in developing research priorities in the supporting standards development. Moreover, it will serve as the foundation for new occupational studies of greater detail and precision."^{2/} They continue, stating that, "within ten years, NOHS as an independent study, will be obsolete. Industry will have access to higher technology; its occupational health characteristics will be correspondingly different."^{3/}

Exposure Characteristics

The surveyors for the NOHS were given instructions to include as exposure any exposure to a carcinogen or exposure to a non-carcinogen whose concentration in a mixture is

^{1/} NOHS, Volume III, December, 1977, page 1.

^{2/} NOHS, Volume I, May, 1974, page 5, introduction.

^{3/} Ibid, page 6, introduction.

greater than one percent.^{1/} Exposures would include dusts, fumes, gases, vapors, solids, liquids or mists.^{2/} Such exposures may either be detectable to the human senses or non-detectable.^{3/} Duration of exposure was only considered as four or more hours of process use per day or not.^{4/} Exposures were considered as existing if they were actual, potential or inferred.^{5/} Exposures were to be considered those that would be existing in the absence of any personal protective equipment.^{6/} The NOHS report well recognizes that its determination is on an exposure-nonexposure model and pays no attention to dose level for exposure.

Sampling Procedures

A further recognized source of error bias in the estimation process is well recognized within the sampling structure as replication was not undertaken at either stage of sampling.^{7/} The first stage sampled Standard Metropolitan Areas (SMSAs) by size. The second stage also stratified by Standard Industrial Classification (SIC) and by size of worker population.^{8/}

^{1/} NOHS, Volume III, December 1977, page 8.

^{2/} NOHS, Volume I, May 1974, pages 18-19.

^{3/} Ibid.

^{4/} Ibid, page 19-20.

^{5/} NOHS, Volume III, December 1977, page 4.

^{6/} NOHS, Volume I, May 1974, page 19.

^{7/} NOHS, Volume III, December 1977, page 3.

^{8/} Ibid.

The second stage sampling was in terms of facilities with at least eight employees excluding those in agriculture, non-petroleum mining, railroad transportation, government agencies and private households.^{1/} The authors indicate that unbiased variance estimates were not available as the sampling was not replicated at either stage of sampling.^{2/} Further, because the second stage units were not selected independently within the first stage units, the authors suspect their estimator may understate the actual sampling variance.^{3/} After the data was collected, extrapolations to the total U.S. workforce were made through the sampling structure.

Study Findings

In total, nearly 4.38 billion exposures^{4/} to 198 specific chemical or physical hazards were identified for 38.2 million employees.^{5/} This would indicate an average of 115 potential exposures per worker, or that each worker, on the average, was potentially exposed to two-thirds of all the specific chemical and physical hazards evaluated. No indication was given of the relative magnitude of risks to workers from these various hazards. However, because of the different rules for defining exposure to carcinogens and to non-carcinogens, the selection of hazards

^{1/} NOHS, Volume III, December 1977, page 3.

^{2/} Ibid.

^{3/} Ibid.

^{4/} NOHS, Volume III, December 1977, Table 50, pages 444-448.

^{5/} NOHS, Volume III, December 1977, Table 1, page 42.

exposure oversampled relatively those exposures that were considered a potential exposure at any concentration -- their presence was indicated -- but for non-carcinogens, their presence was indicated only if their concentration was greater than one percent.^{1/}

Conclusion

The NOHS report is an initial attempt to semi-quantitatively describe the prevalence of various potential exposures in the workplace. From the beginning, its authors recognized its limitations and warned against its misuse. Problems in exposure definition and validation and in sampling bias hurt its utility. It is a recognized imprecise attempt at describing the potential chemical and physical hazard exposures in the work environment in the USA in the early 1970's. That work environment has already markedly changed as a result of technological advancements and regulatory demands. The authors had originally predicted their study would be obsolete in ten years; their expectations are already realized only four years after publication.

The Estimates Paper apparently elected to ignore the warnings of the NOHS Report authors against the potential for misuse of the data.

^{1/} NOHS. Volume III, December 1977, page 8.

APPENDIX C

Arsenic Calculations Contained
in the Estimates Paper

The Estimates Paper (Table 2) contains the following information on arsenic effects (respiratory tract cancers):

Risk Ratio	Age - Adjusted Incidence 100,000 Males 20 Years	Est. No. of Workers Currently Exposed	Expected Excess Cancers
3 - 8	131	1,500,000	3,900-14,000

What these data purport to mean is that occupational exposure to "inorganic arsenic" can cause cancer of the respiratory tract (trachea, bronchi and lungs) at a rate three to eight times that found in non-occupationally exposed persons; that the age-adjusted incidence of such cancers is 131 per 100,000 white males over the age of twenty; that one and one half million persons are currently exposed to inorganic arsenicals in the workplace, and that between 3,900 and 14,000 excess cancers from such arsenic exposures may be expected annually.

These data and projections are flawed for a number of reasons:

(1) The risk estimates are based on studies of past populations with extremely high exposures to inorganic arsenic, some as high as 11,000 micrograms/m³. Not only do such exposures not now occur, but they are expressly prohibited by a recently promulgated OSHA standard which limits exposure to 10 micrograms/m³. 43 Fed. Reg. 19583 (May 5, 1978).

(2) Available data suggest that cancer risks associated with exposure to inorganic arsenic correspond with the duration and intensity of exposure. In the absence of high exposures such risks are minimal.

(3) The 1,500,000 population which is assumed to be at risk is grossly exaggerated and based on old 1964 data cited in the 1975 NIOSH criteria document on inorganic arsenic. OSHA's 1976 Inflationary Impact Statement for the Inorganic Arsenic Standard (page A-42), estimated that there are no more than 7,000 employees currently exposed to inorganic arsenic at levels in excess of 4 micrograms/m³. Indeed, the 1978 arsenic standard calls for controls at 10 micrograms/m³. The number of deaths expected annually by the Estimates Paper authors would be equivalent to the total number of workers exposed.

Further, although more than 40 attempts have been made, arsenic when administered alone, has never been shown to produce cancer of any type in test animals. The only evidence of an arsenic lung cancer theory comes from epidemiology studies: ". . . the relationship between lung cancer and arsenic alone can technically be considered only highly suggestive since other contaminants usually sulphur dioxide have also been present . . ." (EPA, "An Assessment of the Health Effects of Arsenic", External Review Draft, 1978 (emphasis added).) Animal studies have shown that both arsenic trioxide and sulphur dioxide are primary irritants to the lung but not carcinogenic

in animals. Ishinishi, et al. 1977,^{1/} Laskin, et al. 1970.^{2/}
Therefore, any estimates of lung cancer based on arsenic exposure alone are only speculative.

Epidemiologic Studies

Three reasonably good epidemiologic studies have been conducted on inorganic arsenic. Each supports the conclusion that any cancer risk associated with exposure to inorganic arsenic is a function of the duration and intensity of exposure. Only very high exposures have been associated with excess cancers. The three studies are discussed below.

1. Allied Chemical Corporation's Baltimore Pesticide Plant

A study, "Cancer and Occupational Exposure to Arsenic, a Mortality and Morbidity Study of Pesticide Workers," by Mabuchi, K., Lilienfeld, A., and Snell, L.M., from the Department of Epidemiology at Johns Hopkins University, was completed in the first week of September, 1978 and is now "in press". The study analyzes the total and selected causes of death in 240 former employees who died between 1946 and 1977.

The plant produced inorganic arsenic compounds from at least 1919 until 1976, except that copper acetoarsenite

1/ Ishinishi, et al. "Preliminary Experimental Study of Arsenic Poisoning in Rat Lung," at 191-196 in Environmental Health Prospectus, Vol. 19 (1977).

2/ Laskin, et al. 1970 "Inhalation Carcinogenesis," AEC Symposium Series NO. 18 (1970), edited by Hanna, M.G., Jr., P. Nettleheim, and J.R. Gilbert.

(Paris Green) was last packaged in 1946. The peak of production of arsenicals occurred around 1950.

Arsenic trioxide powder was the starting material for producing various arsenical compounds, most of which were ultimately used as insecticides. The arsenic trioxide was shipped into the plant by rail, unloaded, and stored in various locations in the lot surrounding the Arsenic Acid Plant, where the trioxide was reacted with nitric acid. The resulting liquid acid was stored in tanks for production of other arsenicals, or packaged for sales.

Adjacent to the Arsenic Acid Plant, a main three-story structure, the "Insecticide Building", was located, and it was there that various arsenical insecticides were manufactured. Lead arsenate was made by mixing lead-oxide suspended in water with the arsenic acid in a tank on the top floor. The precipitated lead arsenate ran down to drum dryers on the bottom floor. The dried product was screened and then conveyed back to the third floor for milling, packing and bagging. Production processes for other arsenicals were similar.

Before 1952, hygienic control at the Arsenic Acid Plant was allegedly poor and workers in that location often developed skin lesions (keratoses) and other symptoms of arsenism, such as perforated nasal septa. In 1952, the Arsenic Acid Plant was reconstructed and improved personal hygiene practices including daily showers and clothing changes were introduced. Also, in the 1950's a series of measures were taken to improve hygienic

conditions in the Insecticide Building.

Mabuchi and colleagues estimate that the atmospheric concentration of arsenic in the Insecticide Building was at least 1,000 micrograms/m³ during the 1950's, and that in the Arsenic Acid Plant prior to 1952 the highest concentrations of arsenic were at least 5,000 micrograms/m³.

Allied Chemical had files available for all hourly workers hired in 1946 or later and for all salaried employees hired in 1955 or later. For some of those hired prior to 1946 and 1955, respectively, records were incomplete. Of the 3,141 persons employed between 1946 and 1974, 2,189 had been employed for less than four months and, since it was not possible to trace many of them, 441 (a 20% random sample) were followed up. However, of the 952 who were employed four months or longer, all were included in the follow-up study. Thus, the team of 441 who worked less than 4 months, and the 952 who worked more, made a total of 1,393 subjects who were subjected to follow-up. 1,050 were males and 343 females.

For each person, the degree of exposure to arsenicals was graded as "high", "medium" or "low". Those who worked in the arsenic acid area and were near the "Insecticide Building" were assumed to have had "high" exposure; maintenance and shipping workers were assumed to have had "medium" exposure and office workers were assumed to have had "low" exposure. Some "unspecified production workers" were placed in a "possibly high" exposure category. (In summary, of the 1393 records studied, 718

were judged to have had "high" arsenical exposure, 289 "medium" exposure, 234 "low" exposure, and 151 "possibly high" exposure; [one person for whom records were missing was excluded]].

As for the ex-employees themselves, a surprisingly high number of those known still to be alive were able to be contacted. As noted, 240 of the 1393 were known to be deceased on the basis of death certificates which were available to the authors. Of the 901 who were alive in 1977, 745 responded to a questionnaire or gave an interview; nearly 83%. Only 252 of the 1393 (18%) were lost to follow-up, and of these 35 were believed to be deceased but without obtainable death certificates. All of the 38 persons who had worked for more than 25 years and more than 98% of the 142 who had been employed for 5-24 years were traceable. Even among the 20% of those who had worked for less than four months, 76% were traceable.

The statistically significant findings include an excess of deaths from lung, esophageal and lymphatic cancers above the expected numbers in Baltimore City. However, the number of cases of esophageal cancer in these categories were actually only 2 (0.1 expected) and of lymphatic cancer also but 2 (0.2 expected). For respiratory tract cancer the figures are clearly more striking.

There were 13 cases of respiratory tract cancer (6.2 expected) among the 718 employees judged to have had "high" exposure, another eight (5.1 expected) among 266 with "medium" exposure and 2 (0.3 expected) in a group with "possibly high" ex-

posure. The excess is statistically significant at the 5% level only for the "high" exposure group. The figure for expected numbers were taken from the experience of Baltimore City.

Analyzed as a function of date of initial employment, there were 10 respiratory tract cancers (2.5 expected) in the group employed prior to 1946, and 13 (8.8 expected) in the group hired during the eight years between 1946 and 1954. Only in the case of those hired before 1946 is the "excess above expected" significant at the 5% level.

Analyzed as a function of length of employment, there were 3 cancers (1.6 expected) in the 5-24 years group but 9 (1.3 expected) in the 25-plus years group. This last, an observed/expected ratio of 6.78, is a statistically significant excess at the 5% level.

It seems reasonable to draw the conclusion from these data that there is an association between exposure to trivalent inorganic arsenic dust and respiratory tract cancer, and that the association seems to have been dependent both upon duration of exposure and especially, given the history of the plant, upon the intensity of exposure. However, the study does not demonstrate any association between low level exposure to inorganic arsenic and respiratory tract cancer.

2. Asarco, Inc. Tacoma Washington Smelter

A second major report associating exposure to airborne arsenic trioxide to lung cancer is that of Pinto, Enterline, P.E., Henderson, V., and Varner, M.O. (Environmental Health Perspectives,

19:127-130, 1977), who reported on the causes of death among 527 men retired from work at a copper smelter at age 65 after an average duration of employment of 28 years (range 7-54 years). The 527 man cohort comprised those alive as pensioners on January 1, 1949, plus all who became pensioners in the 24 years until January 1, 1973. All deaths were tabulated through December 31, 1973. Death certificates were obtained on all who died.

By using the complete job histories available for 525 of the men and by performing a urinary arsenic determination in 1973 for each of the 1,000 persons distributed among 33 departments in the smelter, the authors were able rather ingeniously to construct retrospectively the exposure index that each man had experienced during his working years. This was done by taking the average urine-arsenic value for each of the 33 departments (as observed in 1973) and by making the assumption that while the magnitudes of exposure in all departments had changed over time, the relative exposure between and among departments had been approximately constant through the years. Thus, multiplication of the average urine-arsenic value for any department by the number of years that a man had worked in that department resulted in an individual exposure index which had no units, but which served as a representative number for comparison purposes.

Another unique contribution of the Pinto article is a graph of results of a study made in 1973 of 24 workers who wore personal monitors continuously for two full days prior to their regular work week, each day during the work week and for three

days following it. (Care was taken to avoid eating fish or other arsenic-rich foods.) Daily urine samples were also collected from each of the men during the test period. The resulting data show a straight line correlation between airborne arsenic concentration expressed as micrograms/m³ and urine arsenic concentration expressed as micrograms/liter. By good fortune, there were available to the authors some scattered air analyses made during the late 1930's and early 1940's showing that the airborne arsenic level in that period was 5 to 10 times higher than in 1973. Thus, it is possible from the published data to approximate the concentration of airborne arsenic to which workers had been exposed during the years around 1940 which was about the time when 50% of the cohort's work experience took place (actual exposures 1910-1973; middle fifty percent of work experience 1928-1947).

The results of the analysis by Pinto and his colleagues show a definite relationship between arsenic exposure index and death from respiratory cancer. The total number of such cancers in the cohorts was 32 versus an expected 10.5, an SMR (Standard Mortality Ratios) of 304.8, significant at the five percent level. The following table from the article correlates exposure indices with SMR. If the indices are plotted against SMR on arithmetic paper, the relationship is roughly linear. See attached graph infra, at C-24.

TABLE I
OBSERVED AND EXPECTED RESPIRATORY CANCER DEATHS AND
SMR BY ARSENIC EXPOSURE INDEX

Exposure Index (mean index)	No. of Men	Respiratory Cancer Deaths		
		Observed	Expected	SMR
2000 (1514)	36	1	0.9	111.1
2000-2999 (2513)	109	4	2.1	190.5
3000-5999 (4317)	205	11	3.9	282.0+
6000-8999 (7473)	109	7	2.3	304.3+
9000-11999 (10,135)	38	4	0.7	571.4+
12,000 (14,712)	29	5	0.6	833.3+

+ means $p < 0.05$

The authors presented their data in another fashion in the table below (see attached graph at C-25).

TABLE II
OBSERVED AND EXPECTED RESPIRATORY CANCER DEATHS AND
STANDARDIZED MORTALITY RATIOS BY INTENSITY AND DURATION OF EXPOSURE

Intensity of Exposure mg/liter urine	DURATION OF EXPOSURE					
	< 25 year			> 25 year		
	Obs.	Exp.	SMR	Obs.	Exp.	SMR
50 - 199	2	2.1	95.2	10	3.6	277.8+
200 - 349	4	1.5	266.7	8	2.2	363.6+
350	3	0.5	600.0+	5	0.6	833.3+

+ means $p < 0.05$

The information in Table II is especially useful in that it shows that while both intensity of exposure and duration of ex-

posure to inorganic arsenic are determinants of respiratory cancer, intensity holding constant for duration is a better predictor than duration holding constant for intensity. This tends to confirm, with considerably more detail, what could be inferred from the Allied Chemical study cited above.

Furthermore, the information in Table II is very important in that it provides an excellent basis for calculating the airborne intensity exposure to inorganic arsenic that is necessary to generate respiratory cancer. Each range of values for urine arsenic shown in the table corresponds to an airborne level range and the latter may be found from the plot of the urine arsenic against airborne arsenic which the authors constructed from their above-mentioned 1973 study of 24 volunteer workers.

Urine arsenic concentrations less than 200 micrograms/liter correspond to airborne levels of less than fifty micrograms/ m^3 . However, it is to be recalled that measurements of airborne arsenic made during the late 1930's and early 1940's were five to ten times higher than those in 1973. Therefore, around 1940, approximately the time when the middle fifty percent of the 527-man cohort had its work experience, minimum m^3 airborne arsenic exposures ranged from 100 to 500 micrograms/ m^3 . It is clear from Table II that persons with this past degree of exposure did not develop respiratory cancer if they worked for less than 25 years. One can, therefore, arrive at the conclusion that no individual in the cohort of retirees who developed cancer had worked in an exposure range of less than 100 micrograms/ m^3 and very many may

have worked at exposures at 2000 micrograms/m³ or more.

3. Anaconda Copper's Smelter in Montana

In justifying its recent rulemaking setting a permissible exposure limit of 10 micrograms/m³, OSHA relied heavily on a 1969 study by Lee and Fraumeni (J. Natl. Cancer Inst. 42:1045-52, 1969) reporting on the mortality experience of 8,047 white male arsenic trioxide-exposed smelter workers at the Anaconda, Montana Smelter who had been employed there for at least one year prior to 1957.

The study reported that from January 1, 1938 to December 31, 1963, 1,877 deaths were recorded. Of these, 147 were deaths from respiratory cancer, a rate 3.3 times the expected rate in Montana. This excess rate was said to be statistically significant at the one percent level.

The cohort which Lee and Fraumeni studied was divided into groups defined by length of service as well as by intensity of exposure. Exposure intensities were designated "heavy", "medium" and "light". The authors stated that "while measurements in work areas may have varied over time, it seems reasonable to assume that these three broadly-defined categories denoting relative exposure remain fixed." In fact, the mean arsenic exposures from 1943-1959 were given by the authors as follows: Heavy (11,000 micrograms/m³), Medium (580 micrograms/m³) and Light (290 micrograms/m³). Thus, the 1969 Lee and Fraumeni study fully supports the analysis made by Pinto et al. (1977) and the conclusions which were derived from it as described above.

4. Summary

To summarize, discussion of three key epidemiologic studies of workers exposed to inorganic arsenic have shown that any excess of respiratory cancer was associated with massive previous exposure, usually to trivalent arsenic trioxide dust, with levels surely in excess of 250 micrograms/m³, but ranging as high as 11,000 micrograms/m³. Collected evidence has repeatedly failed to link low intensity exposure to inorganic arsenic dust with excess cancer of the respiratory tract.

Present Day Occupational Exposure To Inorganic Arsenic

While the Estimates Paper states that 1,500,000 employees are exposed to arsenic, OSHA has concluded in its inorganic arsenic rulemaking that the population at risk is only 660,000. OSHA recognized that the much larger figure (1,500,000), which it explicitly rejected, is out of date and includes many industries which have discontinued arsenic use or which involve exposure to only organic arsenic compounds. OSHA exempted organic arsenic compounds from its rulemaking because of an absence of evidence suggesting such compounds have carcinogenic properties. OSHA concluded:

"4. Employment and Exposure Figures

Employment in all industries directly or indirectly involved in the commercial cycle of arsenic is about 660,000 employees. About 70 to 75 percent of these are production workers and, therefore, potentially exposed to inorganic arsenic. However, a large number of employees included in these figures work in areas where exposures to inorganic arsenicals are very low or

non-existent. Relatively few employees are directly exposed to inorganic arsenicals. Estimates of the number of directly exposed employees working in the affected industries at any one time currently ranges from 1500-1700, for exposure levels of 0.1 mg As/m³ and above, to almost 7000 for exposure levels of 0.004 mg As/m³ and above. Most of the exposed workers are in the copper smelters (especially ASARCO-Tacoma) and wood preserving industries, where exposure levels are also the highest." Inflationary Impact Statement at II-8 (emphasis added).

1. Pesticide Plants

The major source of inorganic arsenical insecticides in the United States during the twentieth century was the Baltimore Race Street Plant operated by Allied Chemical Corporation from 1917 until mid-1976, when it was closed. It has since been razed. As was noted earlier in discussing the Mabuchi study, all of the excess respiratory tract cancer was found in persons hired prior to 1946 and in those who had been employed for more than 25 years. While it is conceivable that a few scattered cases might become evident in the course of the next fifteen years (assuming a "latent period" of approximately forty years), the population from which these cases would have to come is already well past middle-age and numbers only at the very most 300. It may, therefore, be flatly stated that no large contribution is going to be made by Allied Chemical's former plant to any future pool of lung cancer in the United States.

There appear to be only two operating arsenical plants in the United States. These plants, which employ even fewer than the ex-Allied plant, are owned by large and responsible

corporations with sophisticated industrial hygiene departments. One has 17 employees engaged in making arsenic acid from arsenic trioxide; the other has 6 employees who deal with this material which is used to produce organic arsenicals. It may be reasonably assumed that worker exposures have been minimized over the last decade, at least. Promulgation of the recent stringent Standard by OSHA which sets a permissible exposure limit of 10 micrograms/m³ will, of course, obtain. Bearing in mind that Allied's ex-plant in the last forty years appears to have generated an excess of only 9.3 respiratory tract cancer cases compared with Baltimore expected rates (or 14.5 excess cases if comparison is made with United States rates), it is clear that workers in arsenical pesticide plants currently operating are also unlikely to produce a large number of excess cancers in the decades ahead.

2. Smelters

At this time, the major industrial exposures to inorganic arsenic dust is experienced by smelter workers. The reason for this is that practically all ores, especially copper containing ores, are contaminated with trace amounts of arsenic ranging from 0.001 to 5.0 percent, occasionally more. In the process of heating crude ores to the melting point, arsenic trioxide sublimes momentarily into vapor which nearly instantaneously returns to a solid particulate when it meets with air.

There are at this time sixteen operating smelters in the United States (43 Fed. Reg. at 19601). The largest smelter and the one with the potential for the highest exposure is the

one operated by Asarco, Inc. in Tacoma, Washington. This is a "custom" smelting facility which will smelt ores sent to it by others and it is not uncommon for it to deal with ores containing five percent or more arsenic as an impurity. The Tacoma smelter currently employs about 1,000 workers. Assuming, because the data are not readily available, that each of the fifteen remaining smelters employs a similar number of people, it may be stated that there are approximately sixteen thousand persons employed in all of the smelters in the United States.

Lee and Fraumeni, who studied the Anaconda, Montana smelter in 1969, alleged that employees died of lung cancer about 3 times as often as could be expected on the basis of Montana state data. The overall risk ratio for the Asarco, Inc. smelter in Tacoma (Pinto, Enterline et al., 1977) was also about three, and we know that this is very likely the smelter operation with the highest exposure potential. If the experience of the Asarco Smelter is extrapolated to other smelters in the U.S., the maximum number of excess lung cancers they will generate within the next twenty-five years can be estimated. In doing this we will make the (unlikely) assumption that no industrial hygiene improvements have been made in any of these smelters in the past twenty-five to thirty years.

The Pinto, Enterline 1977 study discovered an excess of 22 respiratory tract cancers in 527 retirees of the Tacoma smelter over a 25-year period ending in 1973. If this experience was representative of the other smelters, (undoubtedly an overstatement)

a total of 352 excess respiratory cancers occurred in all smelter retirees in the quarter century between 1949 and 1974. Assuming that the death rate for current workers continues unabated for another quarter century (i.e. assuming that the cancer-preventing effect of the recently imposed ten micrograms/m³ standard will not have an effect for 25 years, and, ignoring evidence provided by Pinto, Enterline et al. which strongly suggests that respiratory cancer risk falls off after cessation of exposure even after many years of chronic exposure), we may at most expect another 350 deaths from respiratory cancer in the next 25 years among smelter retirees. So, on the basis of exaggerated assumptions, one might expect all U.S. smelter workers to generate up to 14 excess respiratory cancers annually for the next 25 years.

3. Other Exposures

Aside from plants that manufacture inorganic arsenicals and plants that smelt ores, there are only a few other major groups who have occupational exposure to inorganic arsenic. This includes certain glass workers^{1/} and carpenters in Hawaii who work with copperchromearsenate (CCA) treated wood. CCA is a pentavalent arsenic derivative which acts as a wood preservative.

^{1/} A recent telephone survey of highly placed technical experts in the glass industry disclosed that of eight of the largest producers of glass in the United States only one still uses minimal quantities of arsenic trioxide at one of its small plants, where, at the most, six people are potentially exposed to arsenic trioxide itself. The survey also confirmed that the absence of arsenic from the glass process has been the case for from 8-20 years.

A study entitled "Cancer Mortality Among Carpenters in Hawaii" authored by Budy, A.M., and Rashad, M.N. of the Department of Genetics and Cancer Center, University of Hawaii, published in the DEPCA proceedings April, 1976, and submitted into the OSHA Inorganic Arsenic hearing record showed that the relative risk for cancer among Hawaiian carpenters exposed to CCA-treated wood is not elevated. The control series comprised carpenters who worked with non-CCA treated wood but whose experience was otherwise the same.

4. Summary

Our estimates of the maximum number of arsenic-induced cancers that the nation may expect to discover during the next quarter century are set out below.

Occupation	Estimated No. of Exposed Employees	Estimated Total No. Excess Cancers	Estimated Excess Cancers Per Year
Smelter Workers*	16,000	350	14
Arsenical Pesticide Workers	323	4	0.16
Glass Manufacturing	6	probably none	0
Hawaiian Carpenters	1,000	0	0
TOTALS	17,329	359	14.16

*This calculation assumes that all 16 present smelters continue to operate. As of this date, one smelter has been at least temporarily shut down. The calculation also assumes that all employees continue to smoke cigarettes at the same rate as in past decades.

Discussion

Returning to the Estimates Paper, the following four statements are made with respect to arsenic, none of which are borne out by the facts:

1. The "Risk Ratio (R)" is "3-8".
2. The age-adjusted incidence [of Respiratory Cancer] per 100,000 males age 20 or older (I) is "131".
3. The Estimated No. of Workers Currently Exposed (N) is "1,500,000".
4. The estimated number of annual cancers attributable to arsenic [(R-1)NI] is "3,900-14,000".

Let us examine each of these in turn.

1. As given, a risk ratio of "3-8" is misleading. The source of the information is cited as Fraumeni, J.F. in the chapter on Occupation in the book Persons at High Risk of Cancer, Academic Press, New York, 1975, pp. 167-184.

The figures are obviously based ultimately upon a study published nearly ten years ago by Lee and Fraumeni (J. Nat'l Cancer Inst. 42, 1045-1052, 1969) of mortality data from 8,047 workers who were exposed during 25 years from 1938-1963 to arsenic trioxide in the course of their work at an Anaconda Copper smelter in Montana. As was described earlier, industrial hygiene measurements taken at the smelter during the critical years 1943 to 1957 demonstrated that workers were exposed to concentrations of inorganic arsenic ranging from 290-11,270 micrograms/m³, massive doses. The cohort of workers exposed to the highest concentrations had lung cancer

mortality up to 8 times the expected rate, while those exposed to the lower range of concentration had 2.1 to 2.5 times as many lung cancers as would have been expected on the basis of all Montana data. For all of the exposed employees the rate of lung cancer averaged three times the expected Montana rate. The portions of the smelter where the highest exposures took place were torn down at least 15 years ago.

The study by Pinto, et al. of retired employees of the Asarco smelter in Tacoma, Washington, where ores containing up to 5 percent contamination with arsenic were commonly worked with demonstrated a lung cancer rate three times the expected. OSHA commented on the data of Pinto when they were first made public at the Agency's April 1975 rulemaking hearing (43 Fed. Reg. at 19589), stating that it

"... is an excellent study and deserves considerable credence. The study was based upon careful follow-up of a group of long-term exposed workers. Exposure indices, based on 1973 values, provided for a maximum utilization of the data. The consistent dose-response relationship between 1973-based urinary arsenic levels and lung cancer mortality strengthens the association of the disease with worker exposures to arsenic. Thus, OSHA accepts the overall findings of excess lung cancer mortality observed in the study."

From the above, it is clear that the best number to use for maximum "Risk Ratio" is 3; representing it as "3-8" is unwarranted and misleading.

2. The figure 131/100,000 which is given as the age-adjusted incidence of lung cancer is attributed to Bridbord, K.

(1978), New Horizons in Occupational Medicine, National Institute of Occupational Safety and Health, Rockville, Maryland. This reference is available only in the form of a xeroxed paper dated May 1, 1978. A telephone call to Dr. Bridbord's office revealed that the paper is an "unfinished draft" and has not yet been published anywhere. Yet more astonishing is that Dr. Bridbord's unfinished draft contains absolutely no mention of any incidence data for any cancers.

The only mention of arsenic in Bridbord's 16-page "unfinished draft" is in some tables appended to it. One of these tables is merely a verbatim copy of the table in Fraumeni's book referred to above in which the "3-8" risk factor was given. It is also notable that Bridbord's (i.e. Fraumeni) list of occupations involving exposure to arsenic is also out of date.

Of perhaps greater significance is Bridbord's Table II, attributed partly to the NOHS, Vol. III, 1977, and again to the same table in Fraumeni from which he had copied his own Table I, as noted. Table 49 of the NOHS report entitled "Estimated Number of Persons Exposed Full or Part-Time to Occupational Carcinogens," specifically omits any mention of arsenic, though it does list asbestos, benzene, chromium, iron oxide, nickel, petroleum distillates and vinyl chloride.

3. Table II of the document under consideration cites in the column "Estimated No. of Workers Currently Exposed (N)" the figure 1,500,000 as the number occupationally exposed to arsenic. NIOSH's 1975 Criteria Document is given as the reference.

Perusal of the Criteria Document reveals, on the bottom of page 14 and continuing on the top of page 15, the following paragraph:

"Some occupations which have or in the past have had potential exposures to arsenic are listed in Table X-2, [9] NIOSH estimates that 1,500,000 workers are potentially exposed to inorganic arsenic, including arsine and lead arsenate." (Emphasis added.)

The bracketed [9] denotes reference to an 18-year old document edited by Gefafer, W.M.: Occupational Diseases -- A Guide to Their Recognition, Publication No. 1097. U.S. Department of Health, Education and Welfare, Public Health Service, 1964, pp. 83-84. A copy of Table X-2 follows.

TABLE X-2
OCCUPATIONS WITH POTENTIAL ARSENIC EXPOSURE

acetylene workers	insecticide makers
acid dippers	jewelers
alloy makers	lead burners
enamel color makers	lead shot makers
enamel workers	lead smelters
arsine workers	leather workers
barbitt: metal workers	lime burners
bleaching powder makers	metal cleaners
boiler operators	metal refiners
brass makers	microalloyed makers
bronze makers	ore smelter workers
browers	organic chemical synthesizers
cadmium workers	paint makers
cattle dip workers	painters
ceramic enamel makers	paper makers
ceramic makers	petroleum refinery workers
copper smelters	pigment makers
defoliant applicators	plastic workers
defoliant makers	plumbers
dimethyl sulfate makers	printing ink workers
drug makers	rayon makers
dye makers	rodenticide makers
electrolytic copper makers	semiconductor compound makers
electroplaters	sheep dip workers
enamelers	silver refiners
etchers	soda makers
farmers	solderers
ferrosilicon workers	submarine workers
fertilizer makers	sulfuric acid workers
fireworks makers	tannery workers
galvanizers	textile printers
glass makers	tanners
gold extractors	tree sprayers
gold refiners	type metal workers
hair remover makers	water wood controllers
herbicide makers	wood sprayers
hide preservers	wood preservative makers
hydrochloric acid workers	wood preservers
illuminating gas workers	zinc chloride makers

from Gefafer [9]

It should be noted that Gefafer's work was intended only to be a rough inventory of sorts and is out of date. _

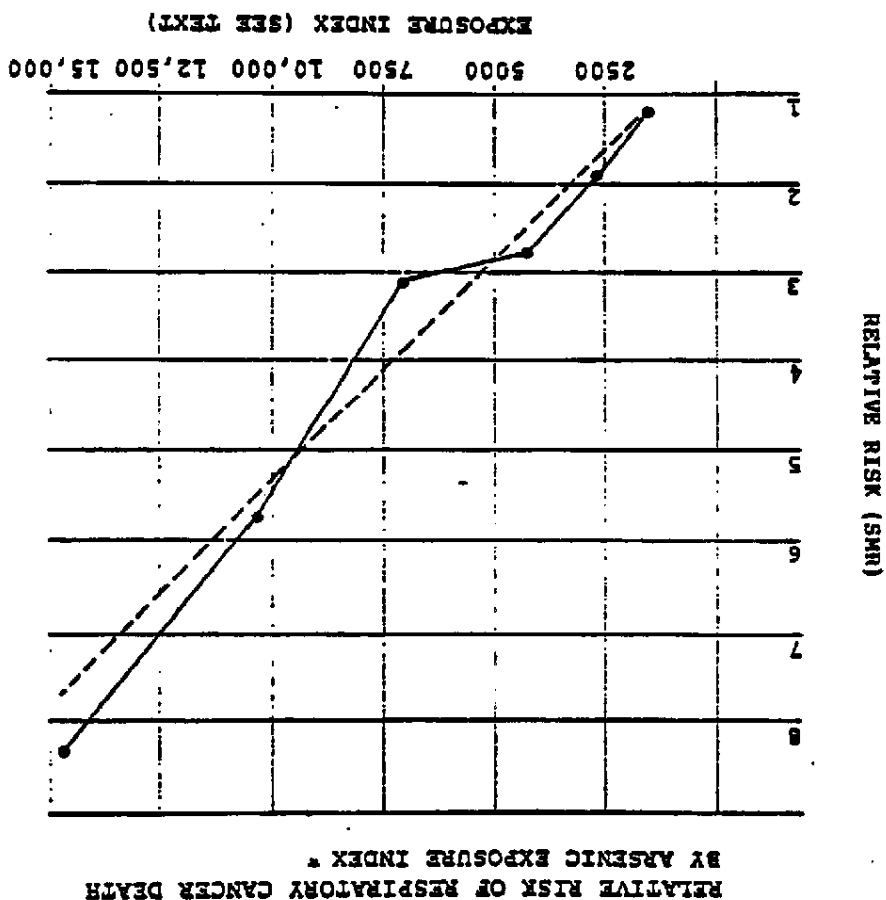
4. This column in the Estimates Paper is headed by "(R-1)NI" which merely means that "R" (Risk Factor) minus one, multiplied by "N" (Estimate Number of Workers) and by "I" (Age-Adjusted Incidence per 100,000 males 20 years) yields a figure for the number of expected cancers each year. We find that the column lists 3,900 - 14,000 as the annual expected number of lung cancers due to arsenic. This figure is without any reasonable support for the reasons discussed above.

In summary, we have shown that to project a factor even as high as 3 over the next 25 years is probably unwarranted. We have shown that the Estimates Paper failed to document the figure 131/100,000 as the age-standardized incidence rate for respiratory cancer, and we showed that the figure for estimated number of workers currently exposed is inaccurate.

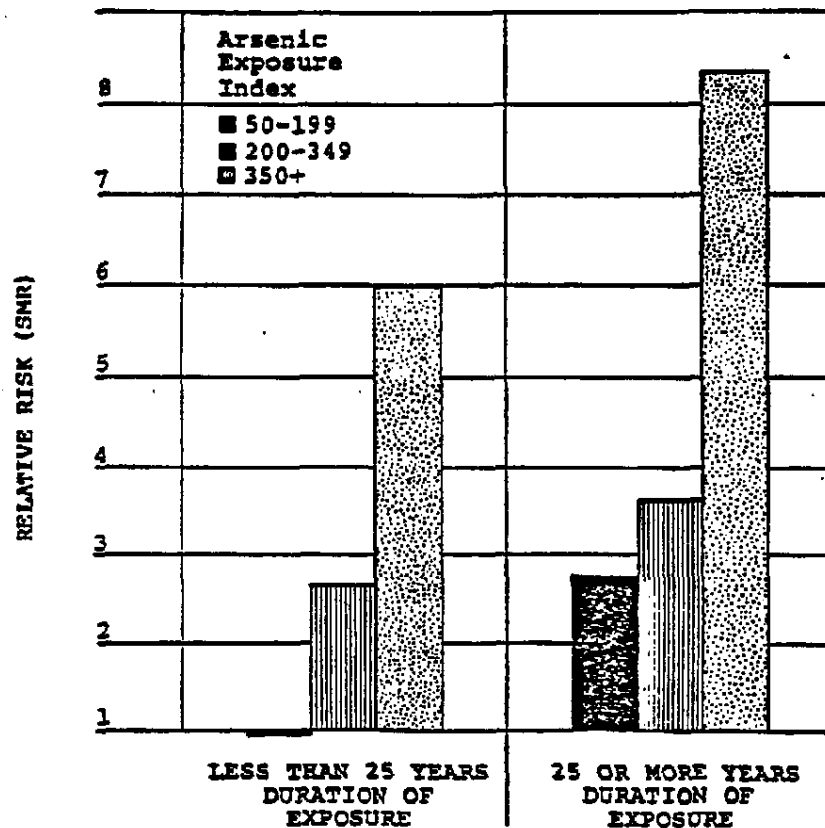
Finally, from an analysis of those occupations where dangerous exposure to inorganic arsenic has existed, we have demonstrated that the number of arsenic-induced cancers to be expected annually during the next quarter century will be no more than 15 because we have weighted every assumption in such a way as to maximize the expected number.

C-24

* PINTO, S.S., ENTERLINE, P.E., HENDERSON, V.
AND VARNER, M.O.
ENVIRONMENTAL HEALTH PERSPECTIVES 19:127-130,
1977



RELATIVE RISK OF RESPIRATORY CANCER DEATH
BY INTENSITY OF ARSENIC EXPOSURE
AND BY DURATION OF ARSENIC EXPOSURE*



*PINTO, S. S., ENTERLINE, P.E., HENDERSON, V.,
AND VARNER, M.O.
Environmental Health Perspectives 19:127-130,
1977

APPENDIX D

Comments on the Estimates Paper With Respect to Chromium

Review of the estimates and the rationale for projecting an incidence of 7,900-16,000 new cases of respiratory tract cancer incurred annually from exposure to chrome and its compounds reveals serious flaws, which are enumerated below:

1) The risk estimate is based on studies of workers heavily exposed in the 1930's and possibly 40's in the manufacture of chromates from chrome ore using the alkali roasting process. Such exposure conditions no longer exist anywhere in the western world.

2) The estimate of population includes workers not shown to be at risk; for example, those engaged in refractory manufacture, in the use of trivalent chromium pigments and the use of trivalent compounds in the tanning industry.

These two points are discussed below.

The Risk Estimate

The report cites Enterline's analysis^{1/} of a cohort of 1,200 workers in three chromate producing plants in the late 1930's. In this study Standard Mortality Ratios (SMR) for lung cancer steadily decreased over the period of observation:

<u>Years</u>	<u>SMR</u>
1941-1945	2909
1946-1950	1570
1951-1955	792
1956-1960	475

1/ Enterline, Phillip E., "Respiratory Cancer Among Chromate Workers," Journal of Occupational Medicine 16: 523-526 (August 1974).

Conditions in these plants improved considerably over the period through 1960 and have since improved. Enterline states in his discussion:

"The old chromate producing plants upon which the American epidemiologic data are based have now been either dismantled or completely rebuilt. For those plants that remain, it is probably too early to find out whether changes made have completely eliminated excess respiratory cancer."

Additional confirmation of a pattern of decreased risks over time was found in a study conducted by Allied Chemical on active and retired employees,^{1/} and reported in the NIOSH criteria document for Chromium VI.^{2/} The study presents SMR's for lung cancer mortality for workers at the Baltimore Chrome Works beginning at different time periods.

<u>Years of First Employment</u>	<u>SMR</u>
1932-1941	680
1942-1951	480
1952-1961	160
1961-1974	<100 (no cases observed)

The authors concluded that a significant downward trend has occurred. This trend accompanies a reduction in dust exposure levels over the years at the plant.^{3/}

1/ Hill, W.J., report submitted to NIOSH, 1974.

2/ Criteria for a Recommended Standard - Occupational Exposure to Chromium (VI), U.S. Dept. HEW, NIOSH (1975), p. 73.

3/ Id.

The most recent revision of this study, now in press, confirms that no cases have been observed after three additional years of follow up. A cohort study commissioned by Allied to the Johns Hopkins University School of Public Health,^{1/} for employees who entered the work force on and after 1945, shows an SMR of about 200 for those employees in the 1945-1950 cohort, with progressive declines thereafter. The post-1960 cohort, with essentially complete follow up, confirms Hill's observation of no reported cases, even though at least one might have been expected from Baltimore vital statistics.

The inappropriateness of applying a relative risk of 5, as does the Estimates Paper, to the population at risk of chromium exposure is further shown by a recent report^{2/} of chrome pigment workers. In this report by Davies, no excess risk was seen among persons with "low exposures" in two factories (exposure dates 1932-1954 and 1948-1967). Nor was excess risk found over all exposure strata in a cohort of workers employed during 1955-1967. Again, some excess respiratory cancer was found among men with early and heavy exposures, but even here the risks were about 2-3.

^{1/} Hayes, Richard B., "A Study of Chromate Production Workers," 1978 PhD (Epidemiology) Thesis, The Johns Hopkins University, Baltimore, Maryland (1978).

^{2/} Davies, Joan M., "Lung Cancer Mortality of Workers Making Chrome Pigments," The Lancet, 1, p. 384 (February 18, 1978).

The Population at Risk

Table 2 of the Estimates Paper indicates that 1.5 million workers are currently exposed to chromium. It should be noted that the source document^{1/} lists only 16% of these jobs as representing any exposure of four or more hours per day.

Furthermore, among the 1.5 million exposed workers are a sizeable number of persons not exposed to those chromium compounds considered to be carcinogenic. The table below, extracted from Table XI-4, page 191-193, of the NIOSH criteria document on Chromium (VI) shows that not all Chromium (VI) compounds show evidence of carcinogenicity. Solubility characteristics served as a major basis for classifying the inferred categories.

TABLE I
NIOSH CHROMIUM (VI) CRITERIA DOCUMENT - 1975

<u>Evident Nontoxicants</u>	<u>Inferred Nontoxicants (see text for basis for inferences)</u>	<u>Evident Carcinogens</u>	<u>Inferred Carcinogens</u>
Sodium bichromate [33, LS Levy, written communication, 1975]	Lithium bichromate	Calcium chromate [3,5, 13,33,41,90,93,94, 98-102,107,119, LS Levy, written communication, 1975]	Alkaline earth chromate and bichromate
Sodium chromate [LS Levy, written communication, 1975]	Lithium chromate	Sintered calcium chromate [108]	Chromyl chloride
Chromium(VI) oxide [33]	Potassium bichromate	Alkaline lime roasting process residue [13]	t-Butyl chromate
	Potassium chromate	Zinc potassium chromate [88,89, LS Levy, written communication, 1975]	Other chromium(VI) materials not listed in this table
	Rubidium bichromate	Lead chromate [68,89]	
	Rubidium chromate		
	Cesium bichromate		
	Cesium chromate		
	Ammonium bichromate		
	Ammonium chromate		

^{1/} National Occupational Hazard Survey - Volume III, Survey Analysis and Supplemental Tables, U.S. Dept. HEW, NIOSH, p. 280 (December 1977).

This table pertains only to hexavalent chromium. Among the other forms of chromium, not all compounds are thought to be carcinogenic. Yet the population represented as at risk includes persons with exposure to those materials not shown to have any increased risk of respiratory cancer.

In summary, the estimated number of deaths from chromium is not accurate because the risk ratio used is not applicable to present-day exposures and because the population considered at risk is inflated by the inclusion of persons exposed to forms of chromium which are not carcinogenic. The only work groups ever shown to have been at excess risk are those involved in manufacture of chromates before 1960, and certain heavily exposed workers in the pigment industry. All told, these two industries account for no more than about 2000 workers in the United States today.

APPENDIX E

Comments on the Estimates Paper With Respect to Nickel

The Estimates Paper has predicted an annual respiratory cancer frequency of 7,300 cases per year from nickel oxide exposure. This number is obtained by using the NOHS estimate of 1.4 million people potentially, inferred, or actually exposed to nickel oxide in U.S. workplaces; a risk ratio of 5 for an excess risk ratio of 4; and an incidence rate of 131 per hundred thousand man years over the age of 20. These three numbers multiplied together give an estimate of 7,300.

The basis for considering nickel oxide carcinogenic comes from a number of papers published in the past. The two major papers are those by Doll, in England, who studied mortality experience of workers from the South Wales nickel refinery^{1/} and Pedersen who studied Norwegian nickel refinery workers.^{2/}

However, more recent studies by Bernacki et al. (see supra, at E-5) have shown no increased association of nickel with lung cancer among workers exposed since WW II.

The Doll Study

Doll demonstrated that the workers, who worked in the South Wales nickel refinery and were exposed to the process of calcination of impure nickel copper sulfide to nickel copper

1/ Doll et al., "Cancers of the Lung and Nasal Sinuses in Nickel Workers," Brit. J. Cancer 24:623-632.

2/ Pederson et al., "Cancer of the Respiratory Organs Among Workers at a Nickel Refinery in Norway," Int. J. Cancer 12:32-41.

oxide, had a high incidence of lung cancer and nasal sinus cancer. He demonstrated analytically that these high risks occurred only in men who were exposed prior to 1930 and did not occur in men who were initially exposed between 1930 and 1945. Mortality was followed up through 1971.

Marked excess of nasal cancers were found in the workers hired before 1930, where 56 to 58 cancers were identified but only .2 were expected. No workers whose initial exposure occurred after 1924 have died of nasal cancer. This is an important cut-off. For, in 1924 cotton masks were introduced to provide personal protection. These were particularly effective against the large particles which would otherwise be deposited in the nose. They were accepted by a high proportion of the men. It is reasonable to conclude that the introduction of this protective measure essentially eliminated the risk of nasal sinus cancer in these workers.

Lung cancer had also been indicated as a high risk in these workers in their early years. These risks continued through 1930 when new processes were introduced in the plant. Within the group of workers hired before 1930, 137 lung cancers were observed and 22 expected for an observed to expected ratio of 6.2. However, only 8 cases have been observed in the 205 men hired since 1929, while five and one half cases would have been expected.

The Pedersen Study

The second study by Pedersen in Norway in 1973 studied the mortality experience of nineteen hundred and sixty men hired

prior to 1961 who had at least three years of employment in the nickel refinery between the years 1953 and 1971. The mortality experience was followed through the end of 1971. In his entire study, he found an overall observed to expected ratio for all respiratory cancers of 5.6 and for lung cancers, of 4.8. The difference is primarily affected by the number of nasal sinus cancers in roasting, smelting and electrolytic processing individuals. Review of these records indicated two cohorts of workers: those hired prior to 1940 and those hired after 1945 through 1960. (The plant was closed down during the war years of 1940 to 1945.) The overall mortality rate from respiratory cancers for the first cohort showed a relative risk of 8.75 and for second cohort of 4.0.

The second cohort should be separated out into those hired before 1950 and those hired after 1950, for major process changes were introduced then which greatly reduced the fume and dust exposure. Unfortunately, the cohort was split at 1955 instead of 1950. Despite this, they have demonstrated that even within that cohort those hired subsequent to 1955 had a lower risk than those hired before 1955. The data is not separated appropriately nor probably of sufficient extent to determine if the excess risk continued significantly past the time of the new process changes.

Present Data Measured Against Estimates

The Estimates Paper does not consider the number of nasal cancers that might now be attributable to nickel exposure.

However, extending its logic should produce an estimate consistent with available data. It does not.

Doll's report indicates 40% as many nasal sinus cancer cases as non-nasal respiratory cancer cases in the nickel workers. Pedersen's report indicates 26% as many nasal cavity cases as non-nasal respiratory cancer cases in nickel workers. Thus, it can be estimated that if 7,300 non-nasal respiratory cancer deaths annually can be attributed to nickel exposure, then [(26-40%) of (7,300)] or 1900-2900 cases of nasal cavity cancer death (page 37) can annually be attributed to nickel exposure. This estimate, however, well exceeds the total U.S. annual nasal cavity cancer incidence of about 800 cases as listed in the Third National Cancer Survey and would indicate all nasal cavity cancers are attributable to nickel exposure, ignoring the other considered causes such as chromium, wood-working, furniture industries, and non-industrial agents.

The Estimates Paper did not include nasal cancers in its projections. In neither of the cited references is a nasal cancer found in a worker whose exposure began recently. In Doll's study, no case was found in a worker beginning after 1924, and in Pedersen's study, no case was found in a worker beginning after 1940. The authors of the Estimates Paper thus probably concluded that at current exposures the risk might be negligible. Similar logic, however, was not carried over to observe the concurrent marked reduction in lung cancer risk. Recent work on U.S. workers exposed to nickel since WW II

has found no increased association with lung cancer.^{1/}

^{1/} Bernacki et al., "Investigation of Exposure to Nickel and Lung Cancer Mortality: Case Control Study at Aircraft Engine Factory," Ann. Clin. Lab. Sci. 8(3):190-194, 1978.

Comments on Estimates Paper
with Respect to Petroleum Distillates

To estimate the lung cancers attributable to Polynuclear Aromatic Hydrocarbons (PNA) exposure, the Estimates Paper inappropriately applies the relative risk of various cohorts of coke oven and gas workers to a wide variety of workers presently exposed to PNA's. The 3,900,000 workers estimated by the NIOSH survey to be exposed to PNA's are employed in approximately 30 industries, including transportation equipment, rubber, petroleum workers, and the printing and publishing industry. The exposures in these industries are very different from the exposures of coke oven and gas workers. In addition to PNA's, coke emissions are composed of such chemicals as arsenic, aromatic amines and ammonia, some of which themselves have been implicated as carcinogens. To use such risk estimates for all workers exposed to PNA's is to misuse data.

The difficulty in applying relative risks from one industry to another may be highlighted by the differences in the relative risks of different subgroups in the same cohort in the same study. See Table 1 below for a list of relative risks of respiratory cancer in different subsets of Redmond's coke plant cohort.^{1/} Note that only in workers working at coke oven sites is the risk higher than 3.0.

^{1/} See Table 1 for reference.

Table 1
Relative Risk of Respiratory Cancer*

<u>Work Site</u>	<u>Ever Employed</u>	<u>Employed 5 years or More</u>
Coke Plant	2.01	2.09
Coke Oven	3.31	3.67
Non-Oven	1.01	0.51

*Redmond, C.K. Epidemiological Study of Cancer Mortality in Coke Plant Workers (1976). 7th Conference on Environmental Toxicology, Dayton, Ohio.

The relative risks derived from Menck and Henderson^{1/} should be viewed with caution. The county studied (Los Angeles) is known for having had unusually high pollution levels. Even though there may have been an occupational component to the deaths, these rates should not be selected for extrapolation across the entire United States. In addition, the study is a cross sectional study and not a cohort study. The strongest conclusions that can be derived from studies with such a design is that certain factors are associated.

Data from other studies in the literature are more applicable to industries composing the exposed group. Tabershaw-Cooper Associates did a cohort mortality study of 10,163 petroleum workers.^{2/} Their conclusion was that although mortality from respiratory cancer increased with increased

^{1/} Menck, H. and Henderson, B.C. 1976 - "Occupational Difference in Rates of Lung Cancer," Journal of Occupational Medicine, 18, 797-801.

^{2/} Gaffey, W. "An Epidemiologic Study of Petroleum Refinery Workers," a study performed by Tabershaw-Cooper/Associates. for the American Petroleum Institute.

exposure, the observed mortality was nevertheless below the expected value in the high exposure group. Further, Lloyd, Decoufle, and Salvin's^{1/} proportionate mortality analysis of 2,604 deaths in the printing industry found a non-significant increase for cancer of the lung and bronchus.

In short, it is incorrect to apply risk factors associated with high-risk PNA-exposed workers to all workers with PNA exposure.

^{1/} Lloyd, J. W., Decoufle, P. and Salvin, L.G., "1977 Unusual Mortality Experience of Printing Pressmen." Journal of Occupational Medicine, 19, 543-550.

APPENDIX G

Comments on the Estimates Paper With Respect to Benzene

The estimate of the number of cases of cancer due to benzene exposure has been based on the study by Infante et al., of the leukemia experience of some of the workers in parts of the two Pliofilm plants in Ohio in 1940-49.^{1/} Infante reported seven cases of leukemia of two different forms among 746 workers. Assuming this had been an appropriately designed study, it would have indicated an approximate four-fold excess relative risk of leukemia among the workers (confidence range of 0.2 to 7).

This study, however, suffered from a number of major design problems that diminish its value as an estimate of leukemia risk from benzene exposure. Firstly, the identification of the seven cases was already known prior to the final formulation of the study^{2/} and, in fact, had been published in the local newspaper before any analysis had been performed. Further, only part of the group exposed to benzene at this industrial site were included in the study. The study reported seven cases among 746 workers, but did not report the fact that

^{1/} Infante et al., "Leukemia in Benzene Workers," The Lancet 76-78, July 1977.

^{2/} "In evaluating reports in the medical literature of the excessive incidence of any given disease, particularly when the authors possess beforehand reasons to anticipate or suspect an excess frequency of that disease, over-estimation due to the incentive feature may creep in." Jandl, J.H., "A Critique of EPA's Assessment of Health Risk Associated with Atmospheric Exposure to Benzene," December 2, 1977, p. 3 (submitted to EPA and Env. Health Comm. of the Science Advisory Board, December 9, 1977).

there were no cases among the 404 other workers in the plant. Had the total working population at that time (1,152 workers) been included in the study, the statistical significance and the measurement of the excess would have been markedly diminished.

Another major problem is that the study presents misleading information on the amount of benzene present in the occupational exposure. The study states that the levels were generally between zero and 10 to 15 parts per million. However, reports from the Ohio State laboratories at the that time indicated levels of 500 parts per million at places where workers were known to spend a considerable amount of time. In addition, reports at that time, and subsequently at hearings, have indicated that the amount of benzene contact at the plant was sufficient for a worker's clothing to still be drenched with benzene when he returned home, direct body contact with benzene liquid was quite frequent, and that containers of benzene very frequently were open and fully exposed to the atmosphere. This amount of exposure is considerably different from zero to 10-15 ppm benzene which was detectable at that time only with very technically sophisticated equipment. Therefore, not only is the relative risk of leukemia artificially exaggerated within this population, but the level of benzene exposure is markedly underestimated, thus vastly increasing the apparent risk of leukemia from a specific dosage.

Further, analysis of the leukemia cases in these two

clusters indicate that the cell-type distribution is quite similar to that which would be expected in a population who died at the ages these cases did. Were there to be a specific cause of a specific type of leukemia among the population, one might assume there would be an excess of one specific type of leukemia which the authors do not claim. Thus, the very study upon which the national estimate of benzene-induced leukemia has been based is seriously flawed in terms of all of its specific and essential components.

Additionally, the last of the six pertinent deaths reported by Infante, et al, occurred in 1961 in an individual exposed in the 1940's. Unmentioned is the fact that no leukemia deaths since 1961 within the United States attributable to occupational exposure to benzene have been reported in the medical literature. Surely, if there is any validity to the Infante study implication that workplace exposures to 10 ppm of benzene or less can produce leukemia, we should have had reports of several such cases in the last 17 years.

Comments On Estimates Paper
With Respect To Vinyl Chloride

Table 1 of the Estimates Paper lists vinyl chloride as a chemical associated with cancer induction in man and shows the target organ to be the liver with indicative evidence of the induction of brain and lung cancer as well. Further, the table estimates the number of employees at risk from vinyl chloride exposure at 2,200,000. The available data suggest a reexamination of these statements.

While vinyl chloride (VCM) has been shown to cause cancer of the liver, the evidence for the involvement of other organ systems is so weak that only cancer of the liver can be used in attempting to assess the carcinogenic hazard of VCM exposure. There are indications of an excess of brain cancers in employees exposed to VCM, but the most complete epidemiological study of vinyl chloride workers, Epidemiological Study of Vinyl Chloride Workers, Final Report, prepared for the Manufacturing Chemists Association by Equitable Environmental Health, Inc., January 1978, casts serious doubt on any causal relationship between VCM exposures and brain cancer. It reports a total of 12 brain tumors, but shows no apparent relationship with maximum exposure or total integrated exposure. Additionally, only four of the 12 brain tumors were confirmed by autopsy or craniotomy, leaving the distinct possibility that some of them may have been metastatic tumors from unknown sites or other non-malignant space occupying lesions.

The evidence for lung cancer is similarly unsettled. In a recent epidemiological study, An Epidemiologic Investigation of Lung Cancer in a Multixenobiotic Occupational Environment by Richard J. Waxweiler, doctoral dissertation (Epidemiology) University of North Carolina, Chapel Hill, N.C. 1978, Waxweiler finds an association between polyvinylchloride (PVC) manufacture and excess lung cancer, but makes the association with PVC dust rather than VCM, thus casting doubt whether this excess, if real, is caused by exposure to the monomer, to mechanical effects from the polymer, the polymer itself, or the soap-like materials which commonly coat PVC particles.

The association between angiosarcoma of the liver and VCM exposure seems unequivocal. - It is, however, noteworthy that in the 25 cases which have occurred in the U.S. and the additional 45 which are reported elsewhere in the world where information is available, there has been in each case the opportunity for repeated exposures to high levels of VCM. That is, in each case, the employee had been associated with the cleaning of reactor vessels or other operations which would occasion exposures to hundreds and sometimes thousands of parts per million (ppm) of VCM. No cases are reported in employees who worked only in those parts of the PVC manufacturing and distribution process where exposures are commonly much lower, that is, regularly below 50 ppm.

It would seem then, that the population at risk of liver cancer from exposure to VCM is no greater than the population en-

gaged in the manufacture of VCM and its polymerization to PVC. This population is a relatively small one. It is estimated at approximately 2,300 employees for VCM and 5,000 employees for PVC in the recent Foster Snell survey (contained in AIHC testimony at the OSHA hearings). The NIOSH estimate of the number of employees involved in PVC manufacture in 1974 is 4,040, Engineering Control Technology Assessment for the Plastics and Resin Industry, March 1978, NIOSH Publication 78-159. These two estimates are in close agreement and surely the total number of employees occupationally exposed to VCM, either in the manufacture of VCM or its polymerization to PVC, does not exceed 10,000 in the U.S.

This number of 10,000 stands, of course, in sharp contrast to NIOSH's estimate of 2.2 million persons exposed. The difference is made up of those persons who are employed in the molding and/or fabrication of the PVC resin into the ultimate end product. This group is so wide and diverse that there has been no thorough epidemiologic study, but a substantial effort in studying this group was made by Chiazzi and Nichols and reported in the Journal of Occupational Medicine, Vol. 19 No. 9, September 1977, pg. 623. This study examined the death certificates on 4,341 deaths which occurred among former employees of 17 PVC fabricators during the period 1964-1973. No cases of angiosarcoma were discovered.

Thus it appears that the one clearly identified human risk from VCM exposure is angiosarcoma of the liver and that it has been observed only in exposures arising from the manufacture

and polymerization of VCM and not from the subsequent fabrication of the polymer into the end use products. It would appear, then, that there should be serious doubt about the usefulness of NIOSH's estimate of 2.2 million as the number of employees at risk and that unless future data indicate otherwise, the correct number of persons at risk from VCM exposure is not more than 10,000.

APPENDIX I

Comments on Appendix A of the Estimates Paper

A fundamental assumption of the Estimates Paper is that for a given exposure cohort, the increased relative risk due to that exposure is constant for the rest of the lifetime. Appendix A was attached to the Estimates Paper in an attempt to provide the theoretical justification for that assumption.

However, Appendix A misinterprets data and develops an analytic explanation irrelevant to the assumption.

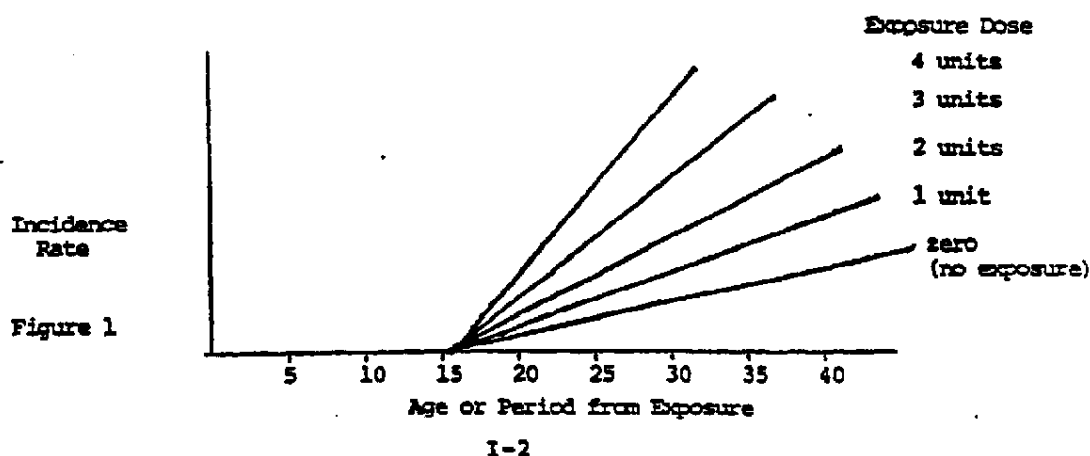
The Appendix provides an explanation for why the incidence rate for exposed cohorts reduces toward that of unexposed cohorts upon withdrawal of some exposures but not of others. The relative risk of lung cancer in ex-smokers (rate for ex-smoker relative to that for non-smoker of the same age) returns toward "1" about five years after cessation of smoking, but the relative risk of mesothelioma (rate for formerly asbestos-exposed worker relative to never-exposed worker of same age) does not approach "1", although both cancers have latency periods that exceed twenty years.

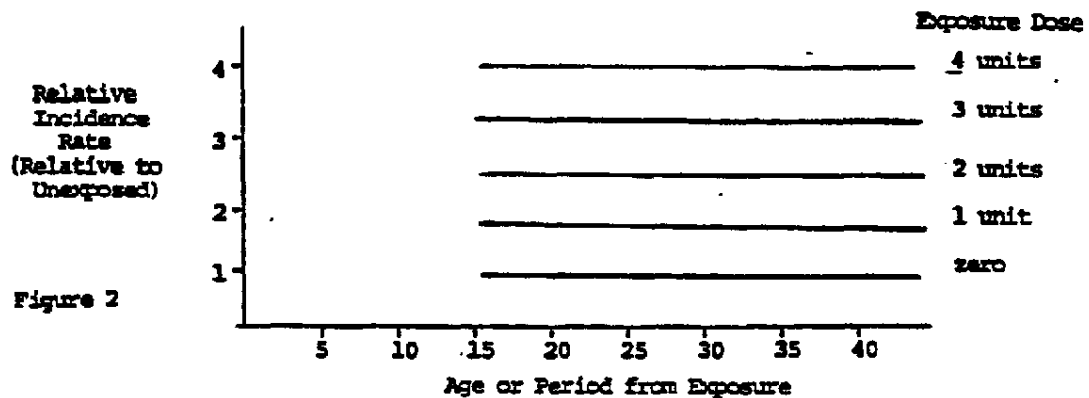
The Appendix, using a multi-stage model of cancer development with some exposure (dose)-dependent stages, develops an explanation. The twenty-year latency periods indicate that some exposure-dependent stages occur early in the development of cancer (some twenty years prior to the appearance of cancer). The lack of a reduction in incidence rates with subsequent reduction of exposure in that cohort indicates that the rate-

limiting steps in the later stages of the cancer development are not exposure-dependent. Asbestos exposure may only be necessary for induction of early stages in the development of mesotheliomas. On the other hand, cigarette smoke may participate not only in the early stages of cancer development, but also in some of the penultimate stages. Thus, cessation of smoking may lead to a return of incidence rate to that expected of non-smokers because the cigarette smoke is not present to participate in those final stages. This is conceptually what the Appendix deals with.

Further explanation of the theoretical support for the assumption is unnecessary, for review of some of the data referred to demonstrates the lack of generalizability of the assumption throughout the area of occupational carcinogenesis.

The assumption holds that for a given exposure level and a given target cancer, the incidence rate in the exposed group will be a constant multiplier of the incidence rate in the unexposed group of the same age or observation period. This model is demonstrated in figure 1 and figure 2.





A review of some of the data cited will demonstrate the inapplicability of the model.

Figure 3 (infra, at I-5) shows Selikoff's data on the observed and expected risks of lung cancers (3A) and of the relative risk in asbestos workers (3B) and the risk of mesotheliomas in asbestos workers (3C). Selikoff's work supports that of Newhouse and Berry in predicting a current markedly increasing risk of mesothelioma in WW II workers exposed to asbestos (3C). However, analysis of his data on lung cancer shows that the lung cancer rates of these workers has leveled and that the relative risk, some 35 years after exposure is rapidly dropping. For neither mesotheliomas nor lung cancers in asbestos workers is there evidence of a constant multiplicative relative risk. In fact, the evidence is to the contrary. Assuming a constant relative risk of lung cancer over the next twenty years for this cohort based on its current or recent lung cancer experience will greatly magnify the risk and is definitely not

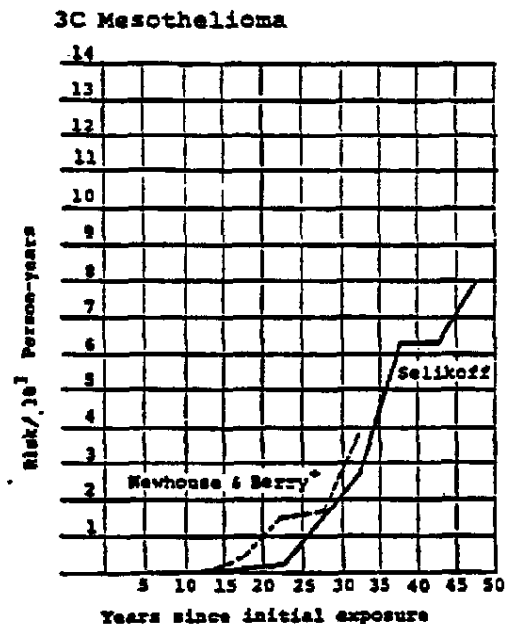
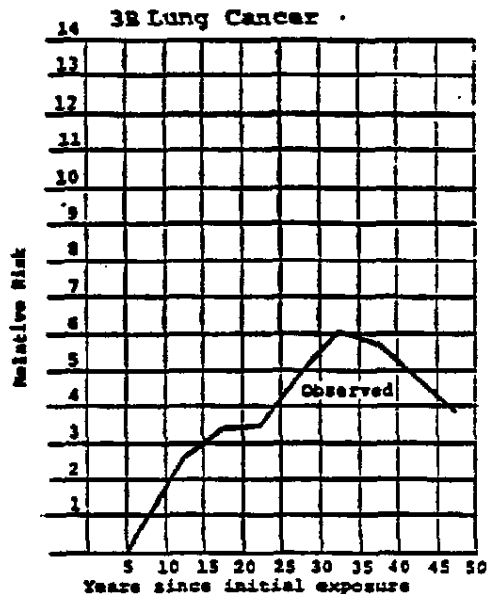
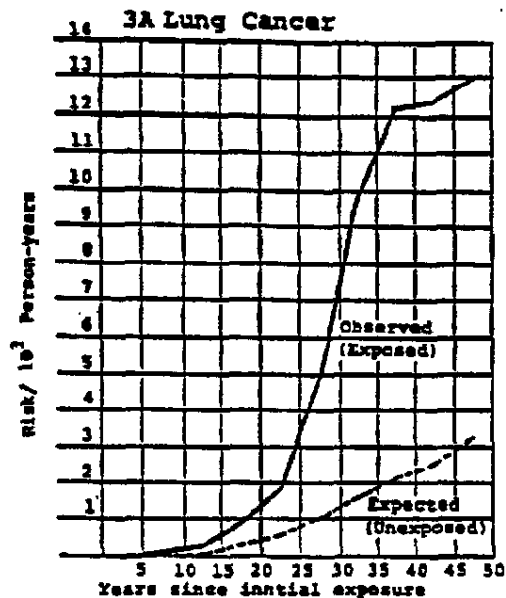
conservative.

For nickel, the evidence from Doll's papers is that the relative risk for lung cancer and for nasal sinus cancer have significantly fallen for successive cohorts over the decades following the reduction in hazard contrary to the Estimates Paper statement on page 3 of Appendix A. Doll does not give sufficient data to examine the behavior over time of the relative risk within each cohort. However, Pedersen does for the Norwegian study.

Pedersen's data analyzed by cohort shows that for all four exposure cohorts, neither singly nor collectively does the "relative risk for lung cancer remain constant for the rest of the lifetime" (under observation). The relative risk for nasal cancer does appear to be constant for the 1930-40 cohort but not for either the 1910-29 cohort nor the entire group. With the exception of the nasal cancers in the 1930-40 cohort, none of the cohorts demonstrate a constant relative risk throughout the period of observation. Contrary to the statement of the Appendix, the Norwegian study demonstrates a marked drop in the relative risk of nasal cancer from 67 in the cohort preceeding the 1950 reduction in exposure to zero in the cohort succeeding the reduction and for lung cancer similarly from 4.5 to 2.5. See Figure 4B infra, at I-6.

Thus, the two examples of occupational carcinogens given in Appendix A do not support the Estimates Paper assumption of a constant relative risk.

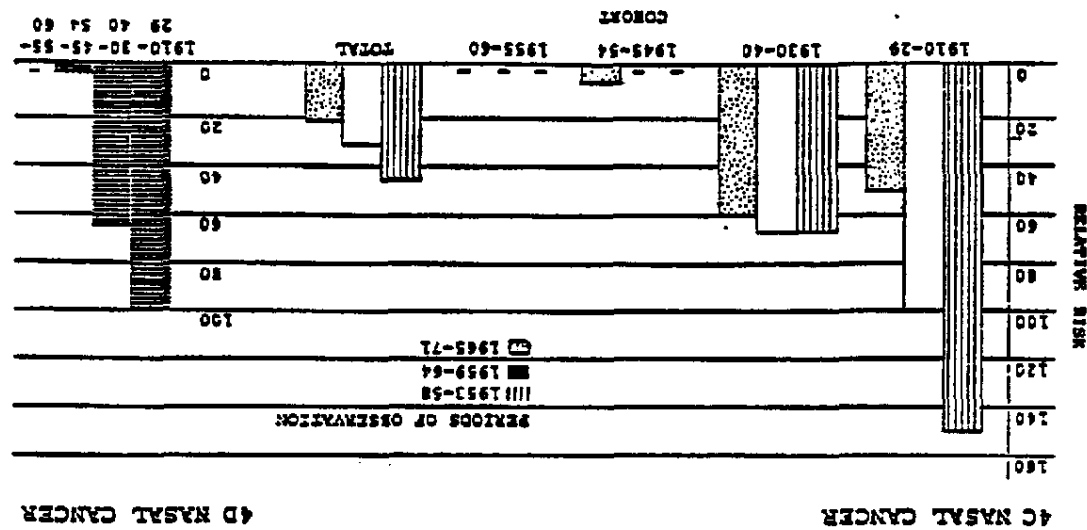
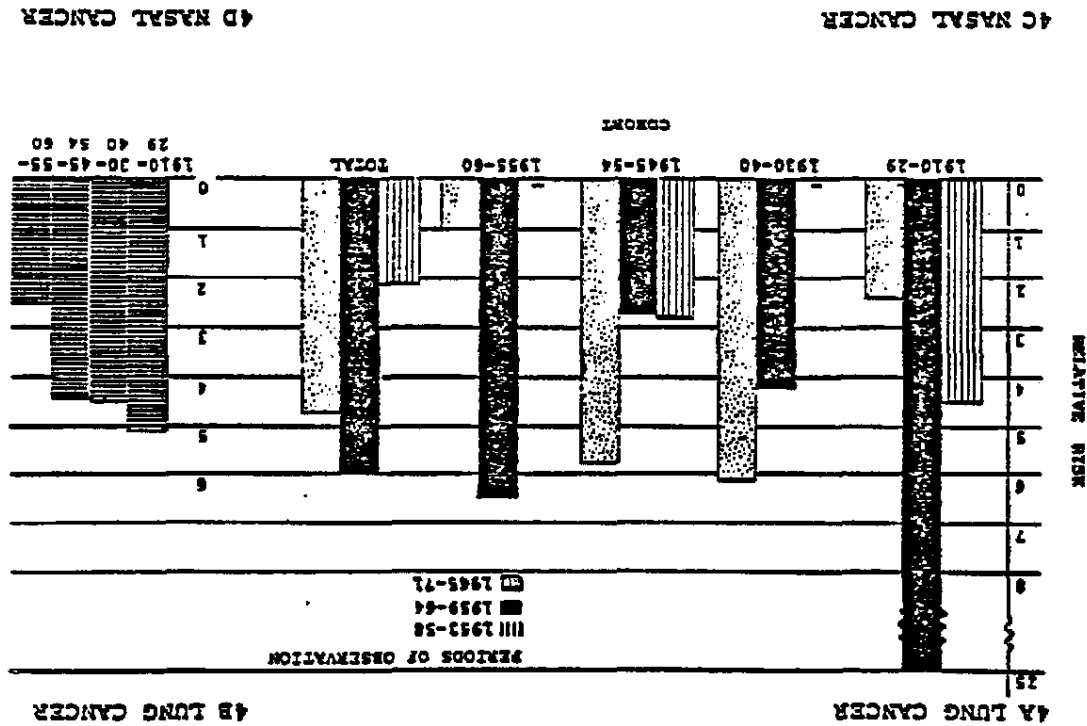
RISK AND RELATIVE RISK OF MESOTHELIOMA AND LUNG CANCER
IN ASBESTOS WORKERS BY INTERVAL SINCE INITIAL EXPOSURE*



* Selikoff, I. and Hammond, E.C., Asbestos-Associated Disease in United States Shipyards. *Can.* 28(2), 87-99 (1978).

+ Newhouse, M. and Berry, G., Predictions of Mortality from Mesothelial Tumors in Asbestos Factory Workers. *B.J. Ind. Med.* 33, 147-151 (1976).

RELATIVE RISK FOR NASAL CANCER AND LUNG CANCER IN
NORWEGIAN NICKEL WORKERS*



PEDERSEN, E., ET AL., CANCER OF RESPIRATORY ORGANS AMONG WORKERS AT A NICKEL REFINERY
IN NORWAY, INT. J. CANCER, 121:32-41 (1973)

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

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September 15, 1978

INCIDENCE OF MAJOR CANCERS POSSIBLY INDUSTRIALLY RELATED
 WHITE MALES
 AGE ADJUSTED (1970 U.S. POP.) PER 100,000

<u>Site</u>	<u>1969- 1971</u>	<u>1975</u>	<u>% Change</u>	<u>Proportion attributed to other possible causes</u>	<u>Total minus "attributable"</u>	<u>1969- 1971</u>	<u>1975</u>	<u>% Change</u>
<u>MOST LIKELY</u>								
Lung	70.7	75.6	+ 7	.85 Smoking	10.6	11.3	+ 7	
Bladder	23.5	27.4	+17	.45 Smoking	12.9	15.1	+17	
Liver, gall bladder & biliary passages	5.6	5.0	-11	?	5.6	5.0	-11	
Lymphoma & Multiple Myeloma	16.1	18.9	+17		16.1	18.9	+17	
Melanoma	4.6	6.3	+37	.75 Sunlight	1.15	1.58	+37	
Subtotal	120.5	133.2	+11		46.4	51.9	+12	
<u>LESS LIKELY</u>								
Intestines & Rectum	51.2	53.1	+ 4		51.2	53.1	+ 4	
Pancreas	12.2	12.5	+ 2	.55 Smoking	5.5	5.6	+ 2	
Subtotal	63.4	65.6	+ 3		56.7	58.7	+ 4	
GRAND TOTAL	183.9	198.8	+ 8		103.1	110.6	+ 7	

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 foreseeable future?" Previously published estimates of this fraction have been as low as 1% to 3% 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 processes have been reviewed. According to a recent

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-causal 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 any 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 chemicals 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.

8⁸

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 foreseeable 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,

* Salikoff (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 constancy 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 ^{Future} ~~current~~ 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 asbestos^V related 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, air-crews, 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 epidemiological 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 would 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, hematopoietic 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 do⁵ 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 will 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 dependant on age and upon duration of exposure, and because most cancers 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.

REFERENCES

1. HIGGINSON, J. 1969. Present trends in cancer epidemiology. Proc. Canad. Cancer Congr. 8:40-75.
2. HIGGINSON, J., and MUIR, C.S. 1976. The role of epidemiology in elucidating the importance of environmental factors in human cancer. Cancer Detection and Prevention 1:79-105.
3. HIGGINSON, J. 1976. A hazardous society? Individual versus community responsibility in cancer prevention. Amer. J. Publ. Health 66:359-366.
4. WYNDER, E.L., and GORI, G.B. 1977. Guest Editorial: Contribution of the environment to cancer incidence: an epidemiological exercise. J. Nat. Cancer Inst. 58:825-832.
5. DOLL, R. 1977. Strategy for detection of cancer hazards to man. Nature 265:589-596.
6. COLE, P. 1977. Cancer and occupation: Status and needs of epidemiologic research. Cancer 39:1788-1791 (Discussion on pp. 1807-1808).
7. COLE, P., and GOLDMAN, M.B. 1975. Occupation. Pp. 167-184 In Persons at High Risk of Cancer (J.F. Fraumeni, Jr., ed.) Academic Press, New York.
8. TOMATIS, L., AGTHE, C., BARTSCH, H., HUFF, J., MONTESANO, R., SARACCI, R., WALKER, E., and WILBOURN, J. 1978. Evaluation of the carcinogenicity of chemicals: A review of the IARC Monograph Programme (1971-77). Can. Res. 38:877-885.
9. SELIKOFF, I.J., HAMMOND, E.C., and CHURG, J. 1968. Asbestos exposure, smoking and neoplasia. J. Amer. Med. Assoc. 204:106-112.
10. ARMITAGE, P., and DOLL, R. 1961. Stochastic models for carcinogenesis. Proc. 4th Berkeley Symposium on Mathematical Statistics and Probability, Vol. 4:19-38. University of California Press, Berkeley.
11. U.S. DEPARTMENT OF HEALTH, EDUCATION AND WELFARE. 1978. Statement of Secretary Joseph A. Califano, Jr. April 26, 1978.
12. INTERNATIONAL AGENCY FOR RESEARCH ON CANCER. 1977. Monographs on the Assessment of Carcinogenic Risks of Chemicals to Man. Vol. 14, Asbestos. (Appendix A, pp. 82-84). Lyon, France.

13. SELIKOFF, I.J. 1978. Paper presented at meeting of the New York Academy of Science, June 1978.
14. SELIKOFF, I.J. 1978. Oral testimony at public hearings on OSHA generic cancer policy, June 1, 1978.
15. SELIKOFF, I.J., and HAMMOND, E.C. 1978. Asbestos-associated disease in United States shipyards. CA 28:67-99.
16. MENCK, H., and HENDERSON, B.E. 1976. Occupational differences in rates of lung cancer. J. Occup. Med. 18:797-801.
17. LASSITER, D.V. 1976. In Occupational Carcinogenesis (eds. U. Saffiotti and J. Wagoner). Ann. N.Y. Acad. Sci. 271: 40-48.
18. BRIDBORD, K. 1978. New Horizons in occupational medicine. National Institute of Occupational Safety and Health, Rockville, Maryland.
19. NATIONAL CANCER INSTITUTE. 1975. Third National Cancer Survey: Incidence data. Nat. Cancer Inst. Monogr. 41:1-454. (S.J. Cutler and J.L. Young, Jr., eds.).
20. NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH. 1977. National Occupational Hazard Survey. Vol. III. Survey Analysis and Supplemental Tables. DHEW (NIOSH) Publication No. 78-114. Cincinnati, Ohio.
21. LEE, A.M. and FRAUMENI, J.F., JR. 1969. Arsenic and respiratory cancer in men: An occupational study. J. Nat. Cancer Inst. 42:1046-1052.
22. INFANTE, P.P., RINSKY, R.A., WAGONER, J.V., and YOUNG, R.J. 1977. Leukemia in benzene workers. Lancet:76-78, July 9, 1977.
23. ROCKETTE, H.E. 1977. Cause Specific Mortality of Coal Miners. J. Occup. Med. 19:795-801.
24. LI, F.P., FRAUMENI, J.F., JR., MANTEL, N. and MILLER, R.W. 1969. Cancer mortality among chemists. J. Nat. Cancer Inst. 43:1159-1164.
25. KOSKELA, RIITA-SISKO, HERNBERG, S., KARAVA, R., JARVINEN, E. and NURINEN, M. 1976. A mortality study of foundry workers. Scan. J. Work Environ. Health 2:suppl. 1, 73-89.
26. GIBSON, E.S., MARTIN, R.H., and LOCKINGTON, J.N. 1977. Lung cancer mortality in a steel foundry. J. Occup. Med. 19: 807-812.

27. MOSS, E. and LEE, W.R. 1974. Occurrence of oral and pharyngeal cancers in textile workers. *Brit. J. Ind. Med.* 31:224-232.
28. LLOYD, J.W., DECOUFLE, P., and SALVIN, L.G. 1977. Unusual mortality experience of printing pressmen. *J. Occup. Med.* 19:543-550.
29. WAGONER, J.K., MILLER, R.W., LUNDIN, F.E., JR., FRAUMENI, J.F., JR., and HAIJ, M.E. 1963. Unusual cancer mortality among a group of underground metal miners. *New Engl. J. Med.* 269:284-289.
30. REDMOND, C.K., STROBINO, B.R. and CYPRESS, R.H. 1976. Cancer experience among coke by-product workers. In Occupational Carcinogenesis. (Eds. U. Saffiotti and J. Wagoner) *Ann. N.Y. Acad. Sci.* 271:102-115.
31. LEMON, R.A., LEE, J.S., WAGONER, J.K. and BLEJER, H.P. 1976. Cancer mortality among cadmium production workers. In Occupational Carcinogenesis. (Eds. U. Saffiotti and J. Wagoner.) *Ann. N.Y. Acad. Sci.* 271:274-279.
32. COOPER, W.C. 1976. Cancer mortality patterns in the lead industry. In Occupational Carcinogenesis. (Eds. U. Saffiotti and J. Wagoner.) *Ann. N.Y. Acad. Sci.* 271:250-259.
33. MONSON, R.R., and NAKANO, K.K. 1976. Mortality among rubber workers: I. White male union employees in Akron, Ohio. *Amer. J. Epidemiol.* 103:284-296.
34. PEDERSEN, E., HOGETVEIT, A.C., and ANDERSEN, A. 1973. Cancer of respiratory organs among workers at a nickel refinery in Norway. *Int. J. Cancer* 12:32-41.
35. DOLL, R., MORGAN, L.G., and SPÄISER, F.E. 1970. Cancers of the lung and nasal sinuses in nickel workers. *Brit. J. Cancer* 24:623-632.
36. ENTERLINE, P.E. 1974. Respiratory cancer among chromate workers. *J. Occup. Med.* 16:523-526.
37. SCHNEIDERMAN, M. 1978. Statement prepared for OSHA hearings.
38. SCHNEIDERMAN, M. 1978. Supplementary statement prepared for OSHA hearings.
39. ACHESON, E.D. 1976. Nasal cancer in the furniture and boot and shoe manufacturing industries. *Prev. Med.* 5:295-315.
40. BRINTON, L.A. 1977. A death certificate analysis of nasal cancer among furniture workers in North Carolina. *Cancer Res.* 37:3473-3474.

41. AKSOY, M. et al. 1974. Leukemia in shoe workers chronically exposed to benzene. Blood 44:837-841.
42. NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH. 1975. Criteria for a recommended standard: occupational exposure to inorganic arsenic. National Institute for Occupational Safety and Health. HEW Publication No. (NIOSH) 75-149. Rockville, Maryland.

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.)

2

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 ^e	— ^d
4-Aminobiphenyl	Occupational	Bladder	Inhalation, skin, oral	100
Arsenic compounds	Occupational, medicinal, environmental	Skin, lung, liver ^e	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	Prostate, 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	Hemato-poietic 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	Hemato-poietic 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 ^d
Chloro-naphazine	Medicinal	Bladder	Oral	_____ d
Carmetholene	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, lung ^e	Inhalation, skin	2,200,000

^aThe main types of exposure mentioned are those by which the association has been demonstrated.

^bThe main routes of exposure given may not be the only ones by which such effects could occur.

^cDenotes indicative evidence

^dNot recorded in the survey: exposure very small in all cases except aflatoxins.

^eNo. of workers exposed to nickel oxide: only about 230 workers exposed to nickel carbonyl

^fExposure 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 ≥ 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 ^e	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 ^g	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: 1.3 - 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 yields 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, Wagonar 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 hydrocarbons (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 PNHs which are contained in petroleum products (Doll, Lloyd, Kawai, Kalzundar, 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 concerns 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 studied 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 (Federsen 1973), the great reduction in exposure 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 ^{decades} ~~decades~~ 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 derived from the widely accepted multi-stage theory of carcinogenesis, wherein 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 ^{the} $(k-1)$ power, as is observed for most epithelial tumors with $k = 5$ or 6 (Whittamore 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 affected. 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 $1 + \frac{c}{k} \left(\frac{t_2}{t} \right)^{k-1}$ (t_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 L.C. 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 implication⁵ 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.

$$\left. \begin{aligned} &1 + c \left(\frac{1}{k-1} \right) \left(\frac{t_2}{t} \right)^{k-1} - \left(\frac{t_1}{t} \right)^{k-1} \\ &\left(\frac{1}{k} \right) \left(\frac{t_2}{t} \right)^k - \left(\frac{t_1}{t} \right)^k \end{aligned} \right\}$$

REFERENCES

- COOK, P.J., DOLL, R., and FELLINGHAM, S.A. 1969. A mathematical model for the age distribution of cancer in man. *Int. J. Can.* 4:93-112
- DOLL, R., MORGAN, L.G., and SPEIZER, F. 1970. Cancers of the lung and nasal sinuses in nickel workers. *Brit. J. Can.* 24:623-632
- DOLL, R., and PETO, R. 1976. Mortality in relation to smoking: 20 years' observation on male British doctors. *Brit. Med. J.* 2:1525-1536
- DOLL, R., MATHEWS, J.D., and MORGAN, L.G. 1977. Cancers of the lung and nasal sinuses in nickel workers: A reassessment of the period of risk. *Brit. J. Indust. Med.* 34:102-105
- FOX, A.J., and COLLIER, P.F. 1976. A survey of occupational cancer in the rubber and cablemaking industries: Analysis of deaths occurring in 1972-74. *Brit. J. Indust. Med.* 33:249-264
- KNOX, J.F., HOLMES, S., DOLL, R., and HILL, I.D. 1968. Mortality from lung cancer and other causes among workers in an asbestos textile factory. *Brit. J. Indust. Med.* 25:293-303
- NEWHOUSE, M.L., and BERRY, G. 1976. Predictions of mortality from mesothelial tumors in asbestos factory workers. *Brit. J. Indust. Med.* 33:147-151
- PEDERSEN, E., HOGETVEIT, A.C., and ANDERSEN, A. 1973. Cancer of respiratory organs among workers at a Nickel refinery in Norway. *Int. J. Can.* 12:32-41
- PETO, J., DOLL, R., HOWARD, W.V., KINLEN, L.J., and LEWINSHOH, H.C. 1977. A mortality study among workers in an English asbestos factory. *Brit. J. Indust. Med.* 34:169-173
- SELIKOFF, I.J., and HAMMOND, E.C. 1978. Asbestos-associated disease in United States Shipyard. *Can* 28(2):87-95
- SMITH, P.G. and DOLL, R. 1978. Age and time dependent changes in the rates of radiation induced cancers in patients with ankylosing spondylitis following a single course of X-ray treatment. Presented at the International Atomic Energy Agency Symposium on Late Biological Effects of Ionizing Radiation, Vienna, March 13-17
- WHITTEMORE, A.S. 1977. The age distribution of human cancer for carcinogenic exposures of varying intensity. *Am. J. Epid.* 106(5):418-432

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

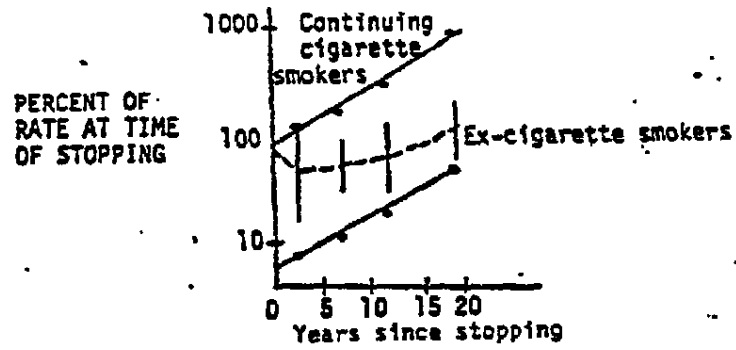


FIGURE 1B

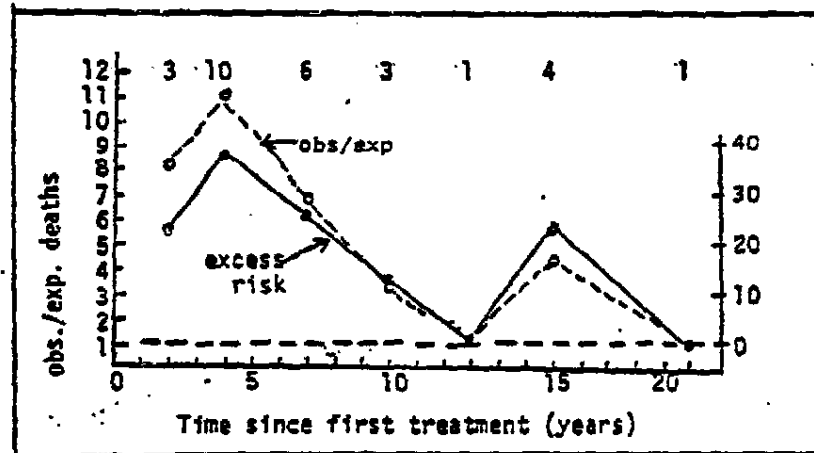


FIGURE 1C

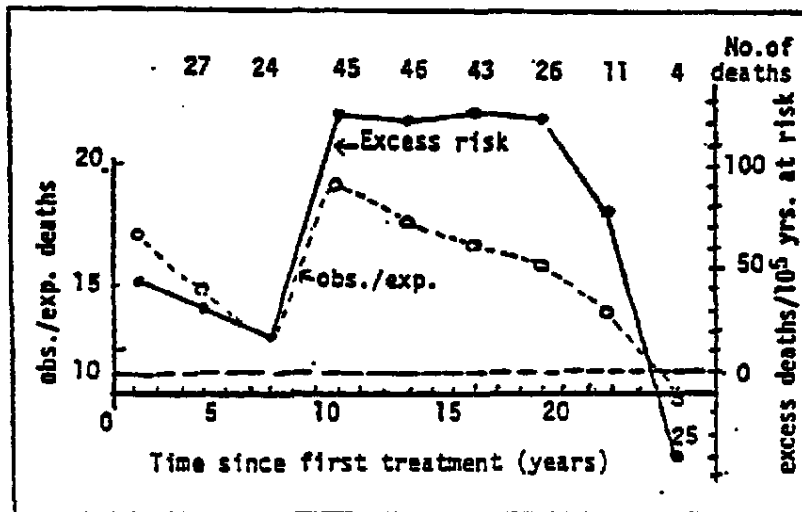
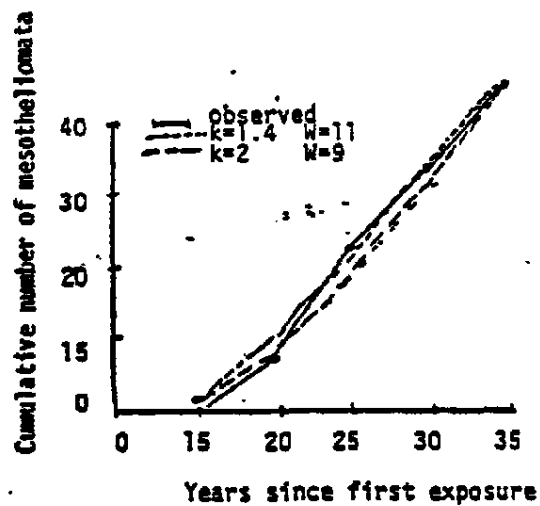


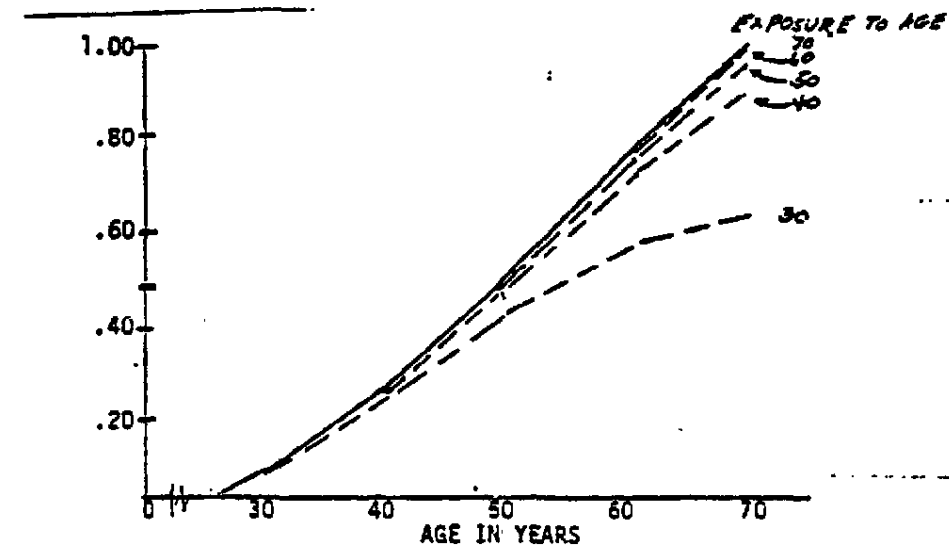
FIGURE 1D



A-5

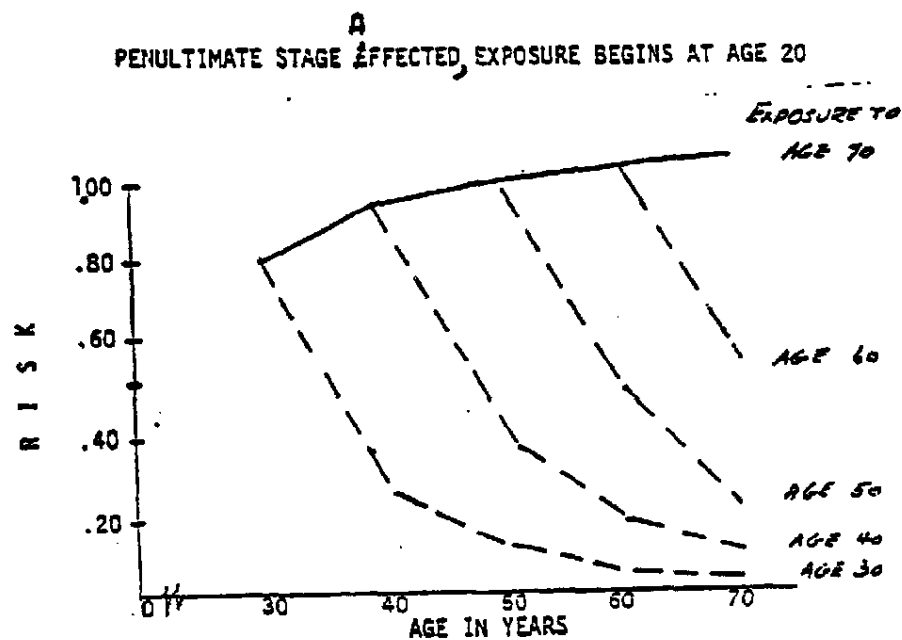
FIGURE 2A

FIRST STAGE ^A EFFECTED, EXPOSURE BEGINS AT AGE 20



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

FIGURE 2B



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

This statement will address the question: "What fraction of the cancer incidence in the United States is attributable in whole or part to occupational exposure to carcinogens in the workplace?" The conventional estimates have been that this fraction is quite small, and figures of between one percent and five percent are often quoted. However, as we will show below, these estimates were admittedly speculative and were incomplete or deficient in several respects. If the full consequences of occupational exposures in the present and the recent past are taken into account, estimates of at least 20 percent appear much more reasonable and may even be conservative.

Basis of the Estimation that 20 Percent of Cancer Deaths
will be Associated with Occupational Exposure to Chemicals

I. Asbestos as a Well-Studied Example

The consequences of occupational exposure to asbestos in the United States have only been fully recognized in the past year. According to estimates made by the U.S. Department of Health, Education, and Welfare, between eight and eleven million 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, while the remainder -- between 6.5 and 8.5 million workers -- were formerly employed in environments with significant asbestos exposure, including 4.5 million who worked in shipyards during World War II. Of these workers, approximately four million are believed to have had heavy exposure to asbestos. Based on epidemiological studies of workers, it is estimated that 20-25 percent of heavily exposed workers die of lung cancer, 7-10 percent of pleural or peritoneal mesothelioma, and 8-9 percent of gastrointestinal cancers. These figures are probably underestimates of lifetime risks, because relatively few workers have yet been followed to the end of their normal lifespan. The total fraction of heavily exposed workers likely to die of these cancers is probably between 35-44 percent.

Of the four million heavily exposed workers, approximately 1.6 million are thus expected to die of asbestos-related cancers. Assuming that the excess risk to the 4-7 million less heavily exposed workers is one-quarter of that to the heavily exposed workers, the total number of cancers associated with asbestos in the less-heavily exposed group would be expected to be about 0.55 million, raising the total to about 2.15 million. Since most of these cancers will be manifested in the next 30-35 years, the expected average number of cancers attributable to asbestos per year in that period will average about 67,000. Such numbers would represent about 17 percent of all cancers detected annually in the United States.

II. Other Less Well Studied Examples

Arsenic

Number of workers potentially exposed: about 1,500,000.
Risk ratios*: 3-8 for lung cancer.
Estimated number of excess cancers per year: 2,100 - 7,300.

Benzene

Number of workers potentially exposed: about 2,000,000.
Risk ratios: 2-3 to 7 for leukemia.
Estimated number of excess cancers per year: 240 - 1,400.

Coal Tar Pitch Volatiles and Coke Oven Emissions

Number of workers potentially exposed: about 60,000.
Risk ratios: 2-6 for cancer of the lung, larynx, skin, and scrotum.
Estimated number of excess cancers per year: 160-800.

* Risk Ratio:

The ratio of cancers to the number expected in a normal population. A risk ratio of two means a doubling of the risk.

Vinyl Chloride

Number of workers potentially exposed: about 2,260,000.
Risk ratios: 200, 4 and 1.9 respectively for
hemangiosarcoma, brain and lung cancer.
Estimated number of excess cancers: 1,940.

A total of 1-3 percent of the cancers occurring in a year
will be associated with these four substances.

III. Substances for which excess cancer incidence has been
recorded but for which estimates of the number of workers
exposed may be less accurate.

Chromium

Number of workers potentially exposed: about 1,500,000.
Risk ratios: 3-40 for nasal cavity and sinus, lung
and larynx.

Estimated number of excess cancers per year: 2,400-
46,000.

Iron Oxide

Number of workers potentially exposed: about 1,600,000.
Risk ratios: 2-5 for lung and larynx.
Estimated number of excess cancers per year: 1,300-
5,000.

Nickel

Number of workers potentially exposed: about 1,370,000.
Risk ratio: 5-10 for lung.
Estimated number of excess cancers per year: 3,800-
5,000.

Petroleum Distillates

Number of workers potentially exposed about 3,000,000.
Risk ratios: 2-6 for lung and larynx.
Estimated number of excess cancers per year: 2,400-
12,000.

A total of 3-18 percent of the cancers occurring in a year
will be associated with these four substances.

IV. Totals.

Thus the total excess incidence would be from 21 to 38 percent. We choose to use the figure 20 percent in order to be conservative.

Summary and Conclusions

1. The oft-quoted estimates that only 1 percent to 5 percent of total cancers in the United States are attributable to occupational factors have not been scientifically documented.
2. Most cancers have multiple causes: it is an error 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, most cancers resulting from exposure to carcinogens will occur late in life: many epidemiological studies detect only a small fraction of early-developing cancers.
4. Past exposure to asbestos is expected to result in over 2 million premature cancer deaths in the next three decades: this corresponds to roughly 17 percent of the total cancer incidence expected in that period.
5. Reasonable projections of the future consequences of past exposure to established carcinogens suggests that at least 8 other substances may contribute substantially to cancer incidence comparable in their total effect to asbestos.
6. The projections suggest that occupationally-related cancers may comprise 20 percent or more of total cancer incidence in forth-coming decades. (This does not include cancers attributable to ionizing radiation.)
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 cannot yet be 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.

APPENDIX

In addition, the following table lists occupational groups in which an excess cancer incidence has been reported without identification of an etiologic agent. When these are fully studied, the overall excess incidence may be assessed.

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
Coal Miners	Stomach	40
Chemists	Pancreas, lymphomas	64 79
Foundry Workers	Lung	50-150
Textile Workers	Mouth and pharynx	77
Printing Pressmen (newspaper)	Mouth and pharynx	125
Metal Miners	Lung	200
Coke by-product Workers	Large intestine, pancreas	181 312
Cadmium Production Workers	Lung, prostate	135 248
Lead Workers	Lung	30
Rubber Industry		
Processing	Stomach, leukemia	80 140
Tire Building	Bladder, Brain	88 90
Tire Curing	Lung	61
Woodworkers	Nasal cavity and sinuses	-
Leather and Shoe Workers	Nasal cavity and sinuses, bladder	5,000 150