AIHC

AMERICAN INDUSTRIAL HEALTH COUNCIL

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11-7-78

~~Dr. Enterline~~ —
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B. D. Dunman

A Reply to:

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

October 23, 1978

PLAINTIFF'S
EXHIBIT
AL-1076

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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 This analysis revealed selective use of data, which was often outdated and of questionable scientific validity.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, expecially 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 =

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

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. 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	3
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.

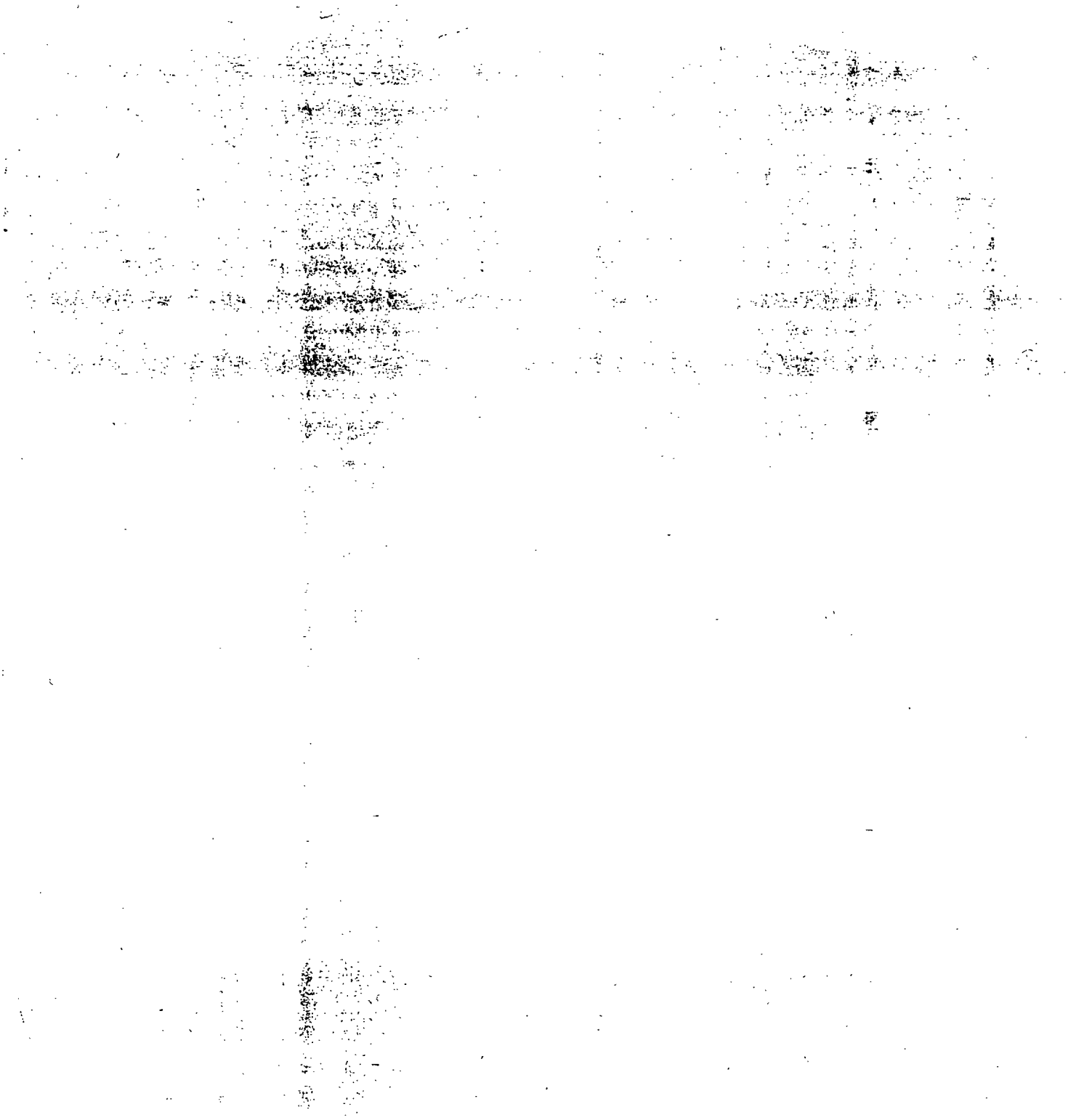
Thus, under the methodology of the Estimates Paper, a double or triple accounting for each death will occur because a person is tallied as dying more than once if he is potentially exposed, for instance, to both asbestos and uranium. The error of double or triple accounting is magnified by use of NOHS 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 anually 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 commmonly 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

Range for Total Exposed and Alive 1978	Total Heavily-Exposed	Surviving WW II Shipyard Workers		
		Heavily-Exposed	Less Heavily-Exposed	Total
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

	1976 Death Rates per 1000 Population	
Age Group	Males	Females
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

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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

	Alive at beginning of 1976		Deaths in 1976		
Sex/Age Group	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) x 131,866 = 75,352) deaths among the heavily-exposed group (.07 x 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) x 131,866 x (.07) x (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	
	7%	10%
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 */

		Years			
SEER Areas	Total	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 unsupportable. 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.)

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

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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

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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

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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 employes.[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

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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 prevalance 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 environemnt 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.

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/m^3. 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/m^3. 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/m^3. Indeed, the 1978 arsenic standard calls for controls at 10 micrograms/m^3. The number of deaths expected annually by the Estimates Paper authors would be <u>equivalent</u> 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 <u>alone</u> 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 Epidemilogy 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

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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. Nettlesheim, 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/m^3 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/m^3.

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 <u>low</u> level exposure to inorganic arsenic and respiratory tract cancer.

2. <u>Asarco, Inc. Tacoma Washington Smelter</u>

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/m^3 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, <u>minimum</u> 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/m^3 or more.

3. Anaconda Copper's Smelter in Montana

In justifying its recent rulemaking setting a permissible exposure limit of 10 micrograms/m^3, 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/m^3), Medium (580 micrograms/m^3) and Light (290 micrograms/m^3). 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/m^3, but ranging as high as 11,000 micrograms/m^3. 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/m^3 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/m^3 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/m^3, 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 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
aniline color makers	lead shot makers
aniline workers	lead smelters
arsine workers	leather workers
Babbitt metal workers	lime burners
bleaching powder makers	metal cleaners
boiler operators	metal refiners
brass makers	nitrocellulose makers
bronze makers	ore smelter workers
bronzers	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	taxidermists
galvanizers	textile printers
glass makers	tinners
gold extractors	tree sprayers
gold refiners	type metal workers
hair remover makers	water weed controllers
herbicide makers	weed sprayers
hide preservers	wood preservative makers
hydrochloric acid workers	wood preservers
illuminating gas workers	zinc chloride makers

from Gafafer [9]

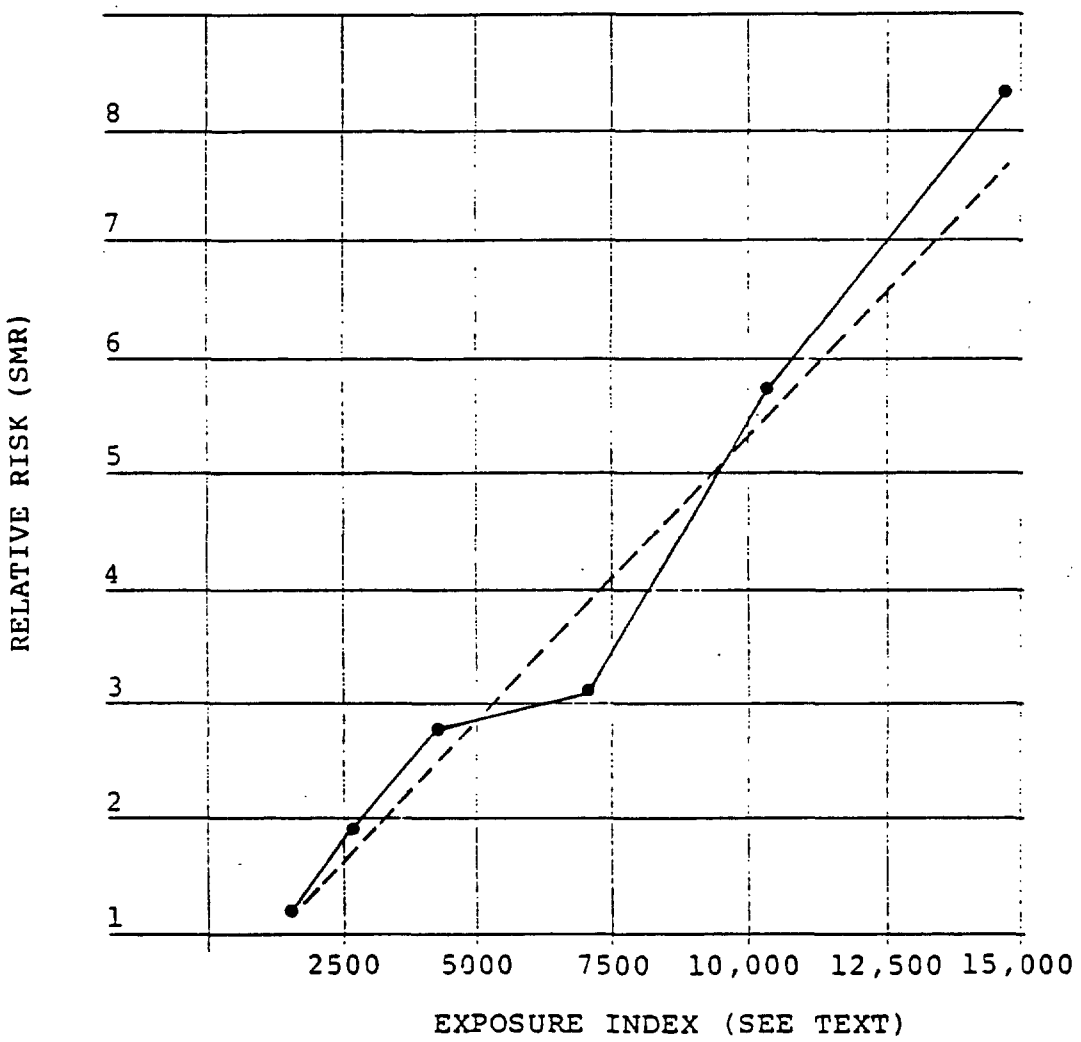
It should be noted that Gefafer's work was intended only to be a rough inventory of sorts and is out of date.

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.

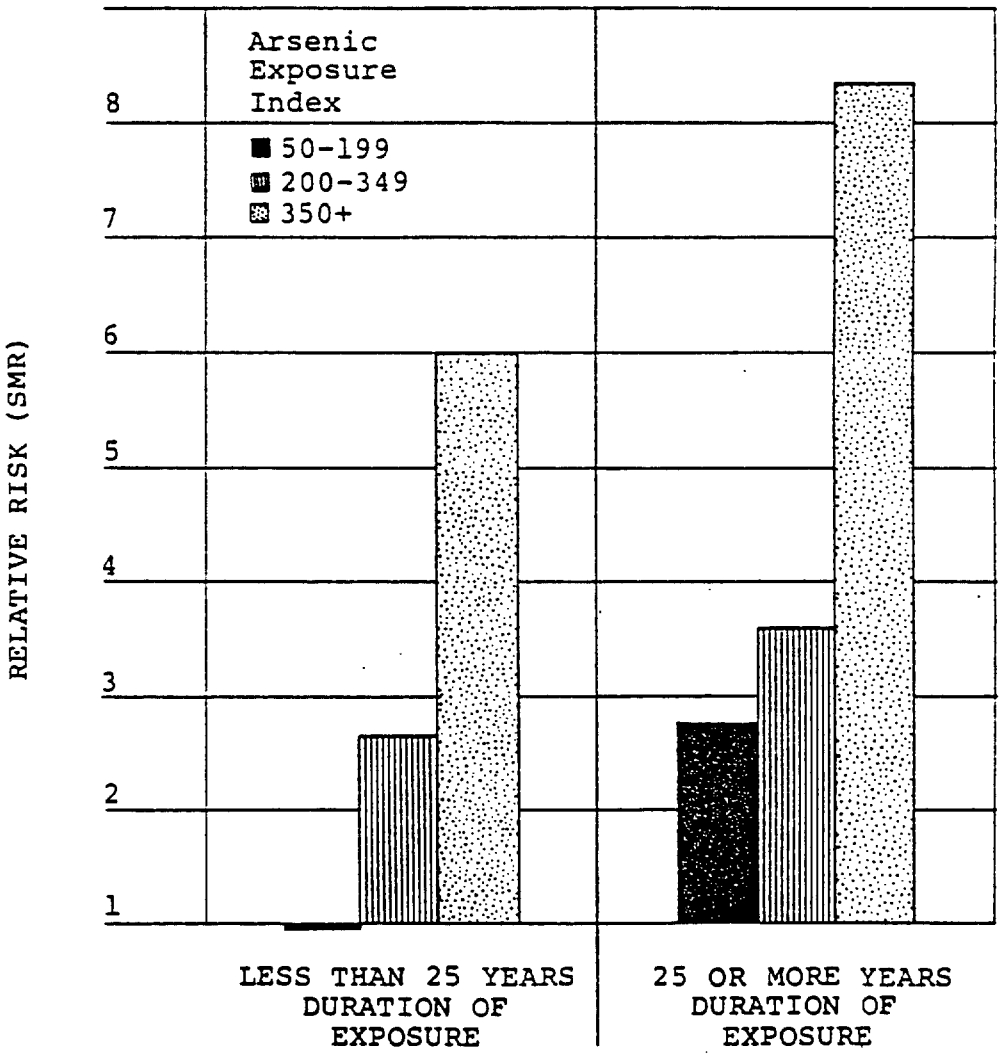
Finally, from an analysis of those occupations where dangerous exposure to inorganic arsenic has existed, we have demonstrated that the number of arsenic-induced cancers to be expected annually during the next quarter century will be no more than 15 because we have weighted every assumption in such a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

RELATIVE RISK OF RESPIRATORY CANCER DEATH
BY ARSENIC EXPOSURE INDEX *



* 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

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:

Years	SMR
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.

Years of First Employment	SMR
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, i, 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

Evident Noncarcinogens	Inferred Noncarcinogens (see text for basis for inferences)	Evident Carcinogens	Inferred Carcinogens
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 communcation, 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 [88,89]	
	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.

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

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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*

Work Site	Ever Employed	Employed 5 years or More
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

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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.

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

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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, overestimation 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 to 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.

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.

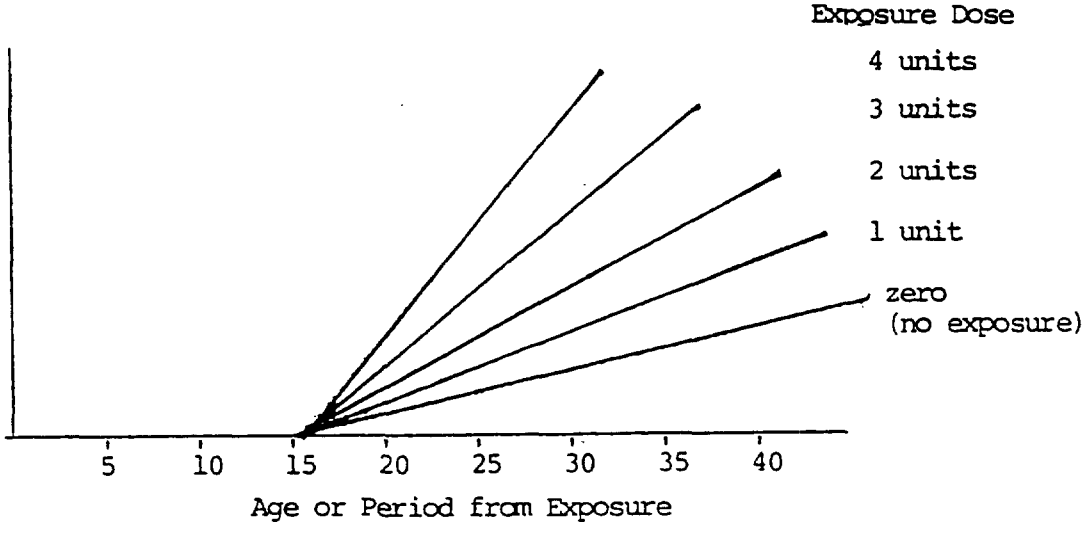


Figure 1

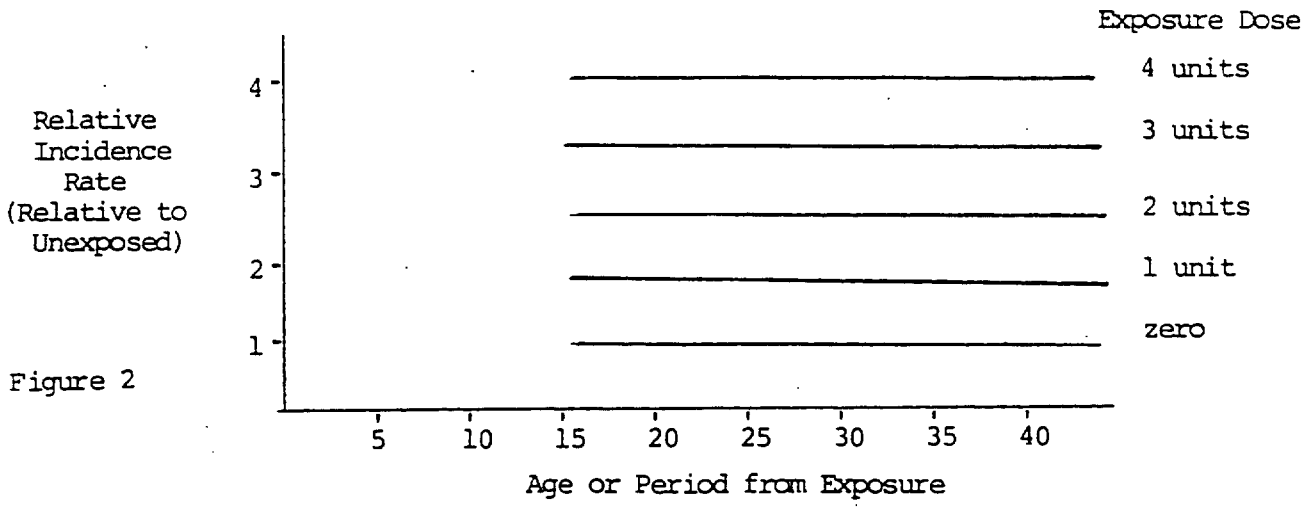


Figure 2

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

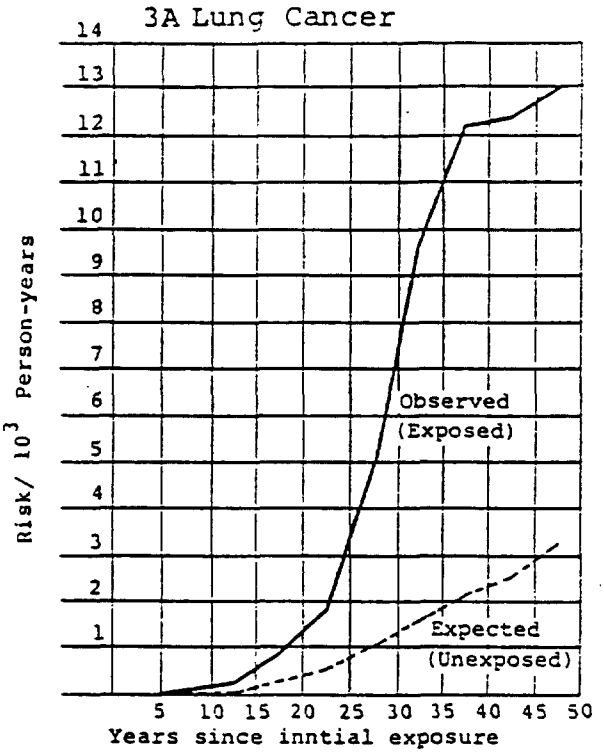
conservative.

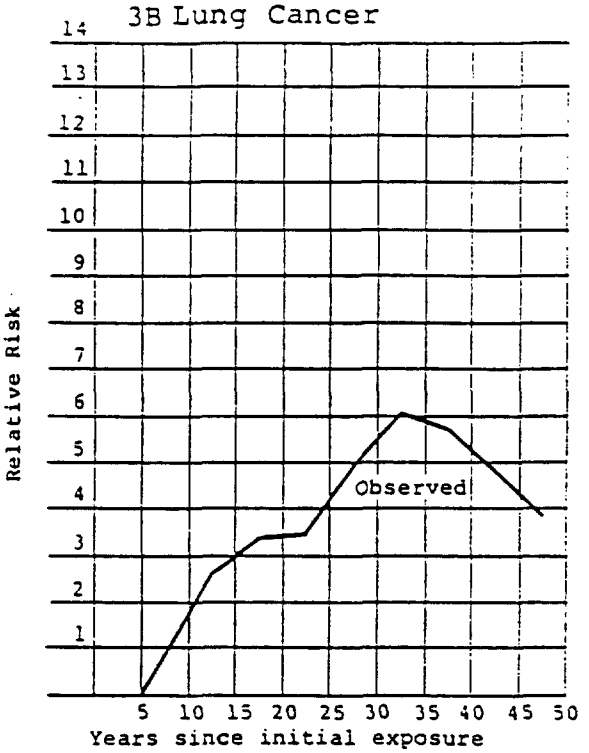
For nickel, the evidence from Doll's papers is that the relative risk for lung cancer and for nasal sinus cancer cancer have significantly fallen for successive cohorts over the decades following the reduction in hazard contrary to the Estimates Paper statement on page 3 of Appendix A. Doll does not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

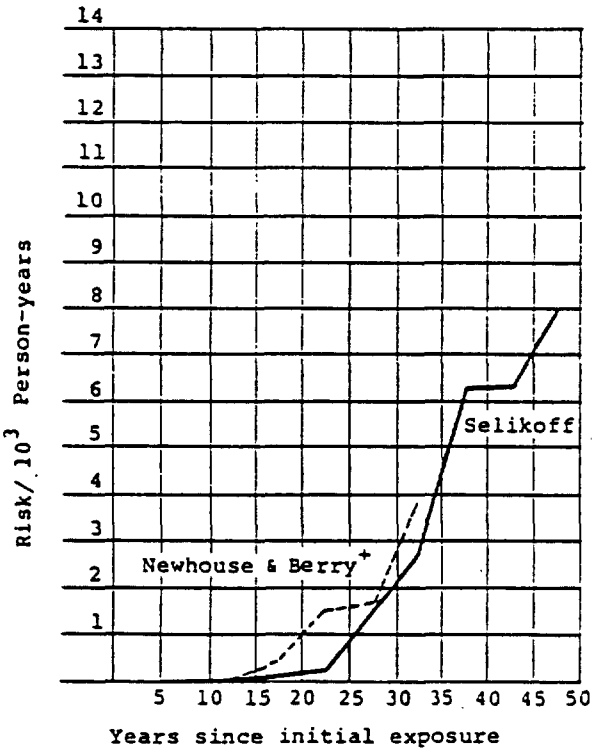
Pedersen's data analyzed by cohort shows that for all four exposure cohorts, neither singly nor collectively does the "relative risk for lung cancer remain constant for the rest of the lifetime" (under observation). The relative risk for nasal cancer does appear to be constant for the 1930-40 cohort 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 thoughout 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*



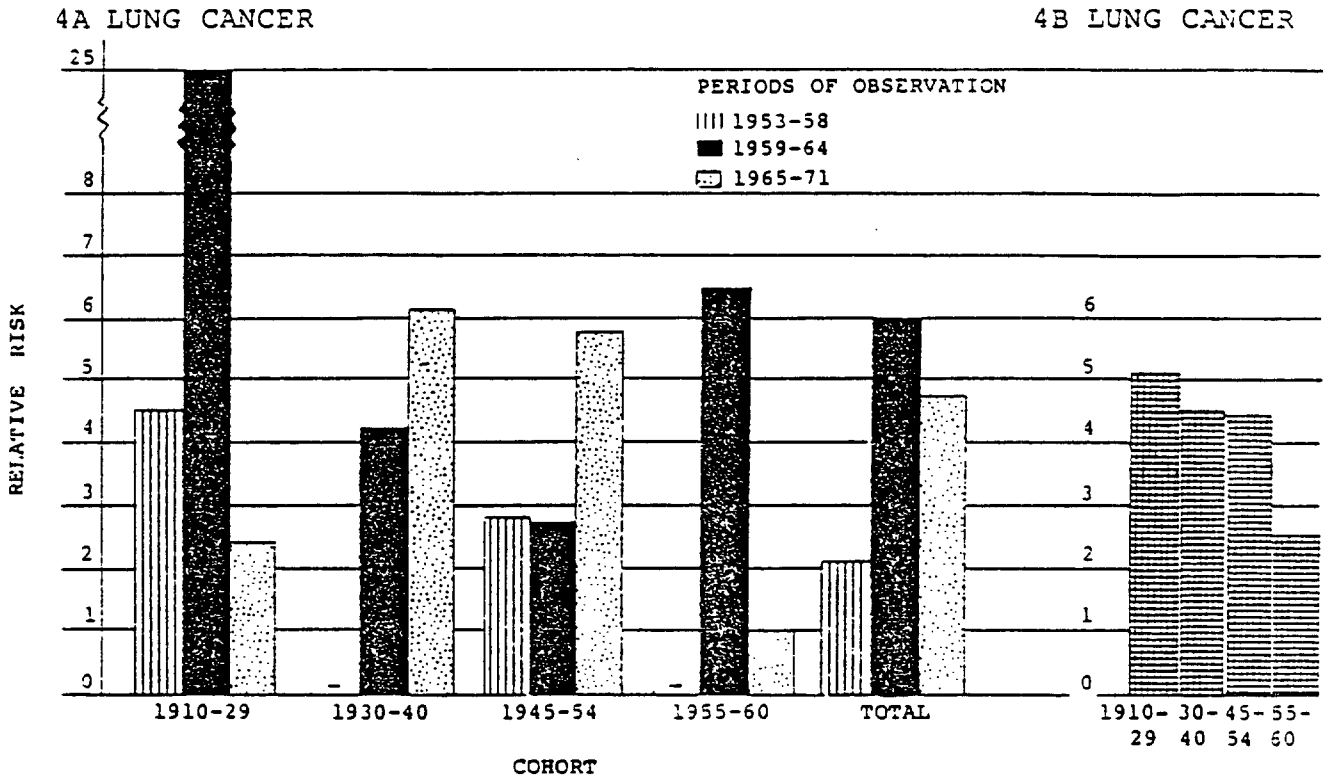


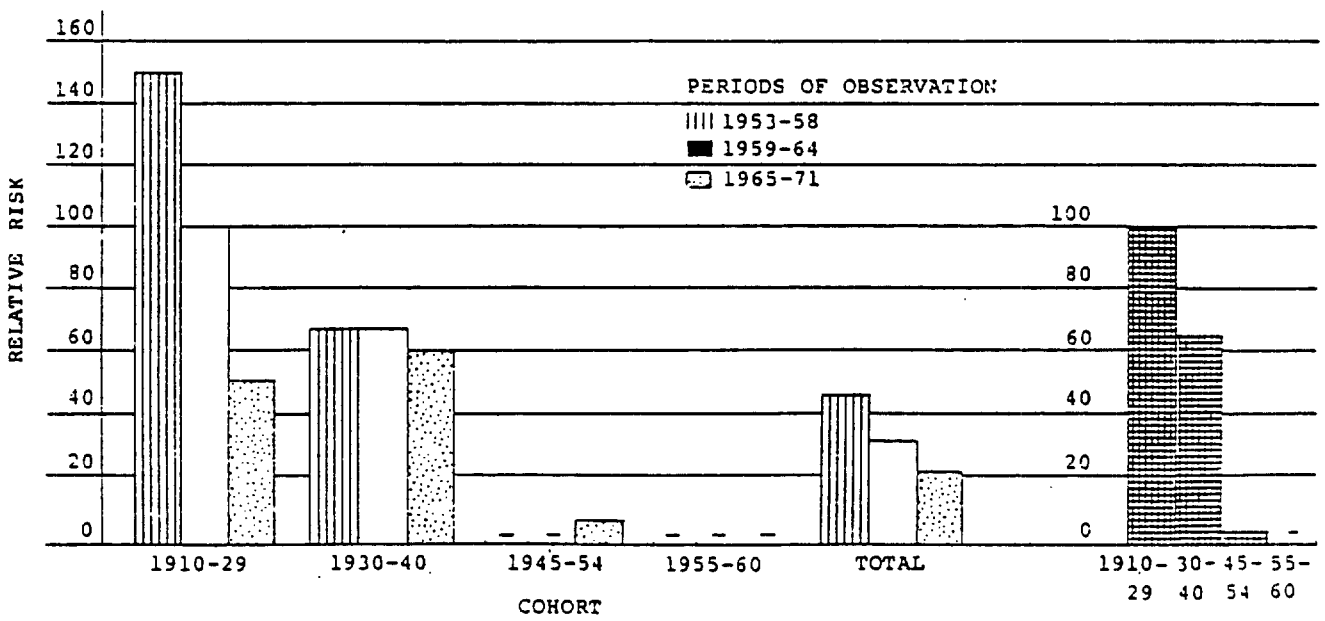


* Selikoff, I. and Hammond, E.G., Asbestos-Associated Disease in United States Shipyards, Ca., 28(2), 87-99 (1978).

\+ 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)

AIHC Reply to Estimates.....9/15/87