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Docket Officer
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Technical Data Center
Room S-6212
U.S. Department of Labor
3rd Street & Constitution Ave., N.W.
Washington, D.C. 20210



Gentlemen:

On October 4, 1977, OSHA published a Notice in the Federal Register proposing a new general regulation concerning the identification, classification and regulation of toxic substances that may pose a carcinogenic risk to workers.

On September 15, 1978, "Estimates of the Fraction of Cancer in the United States Related to Occupational Factors", was prepared and submitted by the National Cancer Institute, the National Institute of Environmental Health Sciences and the National Institute for Occupational Safety and Health as part of the record on the above proposal.

Enclosed are comments on the September 15, 1978 submission of NCI, NIEHS & NIOSH prepared by Paul Kotin, M.D. and G.R. Chase, Ph.D.

It is our intention that the attached comments become part of the record of the OSHA proposal referred to above.

Sincerely,

(Paul Kotin)

PK/pb

COMMENTS ON "ESTIMATES OF THE
FRACTION OF CANCER IN THE UNITED
STATES RELATED TO OCCUPATIONAL
FACTORS" (SEPTEMBER 15, 1978)

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Summary

The dual objective of these comments on the HEW document (prepared by National Cancer Institute, National Institute of Environmental Health Sciences, and National Institute for Occupational Safety and Health) is to first illustrate that the scientific rigor of the document does not justify the speculation that:

"If recent evidence is considered, and if the full consequences of occupational exposures in the present and recent past are taken into account, estimates of at least 20% appear much more reasonable, and may be conservative. These estimates refer to the near term and the future."

"The consequences of occupational exposure to asbestos... over a period of 30-35 years, the expected average number of cancer deaths associated with asbestos per year in that period will be between 58,000 and 75,000. Such numbers would comprise 13-18% of all cancer deaths expected in the United States in the foreseeable future."

The second objective is to enter into the record comments made at a special session of the NCI conference on Cancer Prevention: Quantitative Aspects devoted to the HEW document alluded to above. One of the authors (Paul Kotin, M.D.) participated in this special session, and the quotes that follow at the end of this report are taken from his notes as subsequently confirmed by a taped transcription of the session.

There are two main points in these comments on the HEW speculations:

At first glance, it would appear that only counter-speculation could be used to dispute the speculation in the document, since most of the effects are predicted for the future; and it is alleged that present-day numbers are undoubtedly smaller and

not yet detected. However, perusal of the numbers, citations and logic of the document will readily show that if the prognostications for the WWII shipyard cohort with occupational asbestos exposure are valid, the predicted epidemic should have already been evident in available national cancer surveillance data. Thus, available data refute the speculation for asbestos-related concerns. The asbestos predictions are the cornerstone of the argument in the document, as the "well-studied example." As further evidence of the lack of rigor, the citations in support of the asbestos predictions are incomplete. It will be shown that rigorous use of available evidence contradicts the conclusions of the document.

The second major point of discussion relates to Appendix A of the HEW document. Quoting from the Appendix:

"The purpose of this Appendix is to show that the assumption of constancy of relative risk has a reasonable basis. Both relevant epidemiological data and the predictions of mathematical models of carcinogenesis will be considered."

It is shown by consideration of relevant epidemiological data, the models cited in the Appendix and rigorous data analyses that the conclusions of the report are incorrect. The analyses contained in the report will be shown to be inconsistent with scientifically sound demographic and epidemiologic principles.

The Rigor of the Projections

The HEW report begins with:

This statement addresses the question: "What is the best estimate of the fraction of cancer incidence (or deaths) in the United States that is reasonable to attribute to occupational exposure in the present, and in the foreseeable future?"

and goes on to say that previously published estimates:

"are somewhat speculative and several were seriously incomplete or deficient."

The introduction suggests that the report is going to utilize new evidence and rigorously develop the "best estimate" that will somehow be less speculative than those estimates already in the literature. In fact, the report is, itself, lacking in scientific rigor and results in unsupported and unsupportable speculation.

A rigorous attempt to estimate present and future cancer incidence attributable to any specific carcinogen in the workplace must consider such factors as:

- Reliable estimates of numbers of past, present, and future workers exposed.
- The age and sex of the exposed workers (e.g. the age at onset of exposure.)
- Some indication of the intensity and duration of exposures.

-- The increased incidence attributable (not just associated) to exposures, considering intensity and duration of exposures, latency periods, sex, etc.

Then using established life table techniques, it is possible to speculate on future patterns of morbidity and/or mortality.

Perusal of the HEW statement reveals that the treatment of asbestos, "a well-studied example," is the foundation for the speculation in that document. Thus, a studied review of the treatment of asbestos will give a good indication of the scientific rigor in the entire document.

How many workers have been exposed to asbestos and are living today? The report estimated, without documentation (the reference for the estimate was (11), a statement of Secretary Califano, which in turn cited the HEW report), that:

"Between 8 and 11 million workers have been exposed to asbestos in the U.S. since the beginning of WWII. Of that total, approximately 1.5 to 2.5 million are presently employed. Probably a million have already died, while the remainder -- between 5.5 and 7.5 million workers -- were formerly employed in environments with significant asbestos exposure, including the survivors among the 4.5 million who worked in shipyards during the 1940's."

Although no documentation was given for these estimates, reference (18) (New Horizons in Occupational Medicine, K. Bridbord, 1978) by one of the contributors to the HEW report contains some calculations. Quoting from reference (18):

"A 'back of the envelope' calculation based on exposure to asbestos...An estimated 5 million persons either worked in shipyards during or after World War II. Nearly all of the individuals were exposed to some asbestos, many admittedly at relatively low concentrations, whereas others were heavily exposed. In addition to workers in shipyards, a number of other occupational groups are also exposed to asbestos. The NIOSH National Occupational Hazard Survey estimates that about 1.5 million individuals are currently exposed to asbestos either full or part-time in their work. Assuming a 10% turnover rate each year, it is estimated that at least 5 million individuals may have had significant occupational exposure to asbestos either full or part-time outside of the shipyard industries at some point in their work careers following WWII."

Lacking evidence to the contrary, it appears that the "back of the envelope" calculation was at least in part behind the estimates in the HEW report. While that calculation was properly qualified as "back of the envelope" by Bridbord in reference (18), it hardly represents a "best" scientific effort as alleged in the HEW statement. For example, the NIOSH National Occupational Hazard Survey (NOHS) was initiated in 1972, when the total labor force was 89.0 million. The total labor force in 1946 was 60.5 million (figures available in U.S. Bureau of Census documents). Any rigorous treatment of the past exposures should surely take changing workforce parameters into account. Also, many workers who have been exposed to asbestos to some degree are members of trade unions with very low turnover rates.

Therefore, it is obvious that the estimated number of workers who have been exposed is tenuous.

The HEW document is correct in that asbestos is a well-studied example. Cohorts of miners and millers, factory workers, (including textile workers, asbestos-cement products workers, friction products workers, and others), insulation workers, neighborhood exposures, retired workers and others have been studied and reported in the literature. Furthermore, workplace exposures have been reported in the literature, and OSHA has been sampling for compliance for several years. The citing of only a few heavily exposed cohort mortality studies, while ignoring the wealth of data available for a more scientifically sound speculation, is hardly a best estimate. The well-documented dose-response relationship between asbestos exposure and asbestos-related disease, lung cancer resulting from synergism between smoking and asbestos exposure, spectrum of high to low exposures of the past and different cohort mortality experiences are not utilized in the HEW report.

If the statements in the HEW report are taken at face value, then:

"Most of the predicted effects are to be in the future. An estimate of the present-day numbers of cancers attributable to asbestos would undoubtedly be smaller."

and:

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

would leave no choice but to dispute the HEW future speculation with future speculation.

However, there is an opportunity to refute the speculation in the document by using the logic and numbers in the document itself to show that predicted mesotheliomas are out of accord with observed mesotheliomas from NCI programs.

Reason (a) on page 10 of the HEW document states:

"Two of the major types of asbestos-related cancer, pleural and peritoneal mesothelioma, are not classified as such in the National Health Statistics, but are usually listed as lung cancers or as various abdominal cancers, respectively;"

While there are additional reasons why the national mortality statistics cannot be used for a rigorous investigation of mesothelioma, the above quote from the HEW statement is correct. However, there are data, rigorously documented, indicating the U.S. mesothelioma incidence from 1969 through 1976. The Third National Cancer Survey was conducted from 1969 through 1971. In 1972, a national survey of U.S. pathologists was conducted by McDonald and McDonald (See Preventive Medicine, vol. 6, pages 426 - 446, 1977). The SEER program was initiated in 1973, with data now available through 1976.

Mesothelioma, a rare tumor in the general population, is commonly found in heavily exposed asbestos groups. Thus, it is known as a marker or identifier tumor for cohorts at increased risk because of heavy exposure to asbestos. (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, pp. 620-623. Hoover and Fraumeni, co-authors of the article, are also contributors to the HEW report.)

As a check against the accuracy of the predictions in the HEW statement, it is useful to estimate how many marker mesotheliomas would have been predicted for the U.S. in 1976, using the reasoning and figures in the HEW report itself.

Recall that the HEW report estimated that 4.5 million workers were exposed to asbestos in WWII shipyards. Let us consider the 4.5 million WWII shipyard workers and suppose the probable million who have already died came entirely from that group, leaving an estimated 3.5 million WWII 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 WWI and still alive in 1978 (8 to 11 million, minus one million dead, according to the HEW report), 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 WWII shipyard workers? Since the HEW document estimated 7 to 10 million surviving workers have been exposed to asbestos since the beginning of WWII, it follows that $4/10$ to $4/7$ of surviving workers have had "heavy exposure." Since much of the "heavy exposure" took place during WWI, 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 1

Conservative Allocation of Surviving WWII
Shipyard Workers to Heavily Exposed Category

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

Therefore, a conservatively low estimate of heavily exposed surviving WWII shipyard workers would be between 1.4 and 2.0 million. Virtually all of these WWII workers would have been in their mid-fifties 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 WWII was female. To allow for the fact that age-specific mortality rates are higher for males than females, increase the female proportion in the surviving WWII shipyard workforce from an initial one-third to 40% (i.e. females will have died at a slower rate, thus increasing the proportion of females among the survivors.) 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 2

White Age-Sex-Specific Death Rates, 1976

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

In 1976, in the 55 and over age groups, slightly over 50% of the males were 65 and over, while over 56% of the females were 65 and over. Therefore, allocate 50% of the surviving WWII males to each of the two age groups in Table 2, and 45% and 55% to the 55-64 and 65+ female age groups, respectively. The following calculations can now be made:

TABLE 3

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

<u>Sex/Age Group</u>	<u>Alive at beginning of 1976</u>		<u>Deaths in 1976</u>		
	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 WWII shipyard workers are males, and 50% of the males are 65 and over, we get:

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

in the 65+ age group at the beginning of 1976. (Recall that no deaths were allowed in 1977, to be conservative. If 1977 deaths were to be taken into account, the number alive and at risk in 1976 would

be larger.) Applying the age-sex specific death rate of 67.1 per thousand from Table 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 document apply? According to the references cited in the document (e.g., reference (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 1 the conservative allocation of past heavy asbestos exposure to the surviving WWII shipyard cohort. If 2,000,000 were heavily exposed (derived from the assumption of 7,000,000 surviving in 1978 in Table 1), it follows that of the 131,866 deaths, 4/7 will have been from the heavily exposed group (since 4/7 of the surviving 3,500,000, or 2,000,000 were heavily exposed). Thus at least 7% of the $((4/7) \times 131,866 = 75,352)$ deaths among the heavily exposed group $(.07 \times 75,352 = 5,275)$ will have been due to mesothelioma. The document assumed that:

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

Applying the 1/4 excess risk, we get:

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

TABLE 4

1976 Mesothelioma Deaths Among WWII Shipyard Workers

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

*1/4 for the less heavily exposed subcohort.

Using the figures in the HEW document, thus far we have:

- Conservatively allocated the survivors to the cohort of the WWII shipyard workers,
- Conservatively allocated the heavy exposures to the WWII shipyard cohort,
- Dealt only with the WWII 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 document is applicable to the surviving WWII shipyard workers, the death rates should be increased by at least 40%, increasing the lower bound to between 7,000 and 8,400.

What was the actual incidence of mesothelioma in 1976? (Incidence and mortality are essentially the same for mesothelioma.) The

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

TABLE 5
Incidence of Mesothelioma for All
Sexes and Races -- All Sites

SEER Areas	Years				
	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 yet in SEER program 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 document 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. (If the ship-building of the five areas is taken into account and the logic of the HEW document is followed, the 950 estimate would probably be too high.) Therefore, if there should be at least

7,000 to 8,400 deaths from the WWII shipyard cohort alone, the lower bound for the estimate is at least an order of magnitude too high.

Any suggestion that incomplete diagnostic ascertainment would account for at least an order of magnitude is unsupportable. The article by Blot et al referred to earlier in these comments, co-authored by two of the contributors to the HEW report, 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, 426-446, 1977): Reporting on a mesothelioma survey of pathologists in Canada, the authors found only 37% of the reported cases in Quebec accepted by the Mesothelioma Panel of the Canadian Tumor Reference Centre, compared with 60% for the rest of Canada.

Thus far we have dealt only with a conservative lower bound for mesothelioma using the figures in the HEW report, but only the estimated survivors from the WWII 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 WWII if one accepts the logic set out in the HEW statement. Since the "probable dead" have already been taken into account by allocating all of them to the WWII shipyard cohort, it follows that any calculations based on the

numbers put forth in the HEW report would assume all WWII non-shipyard workers alive and at risk in 1976. Using the "back of the envelope" calculations from Bridbord, 1978 (reference (18)), approximately 1,500,000 would make up the WWII non-shipyard subcohort. The addition of that cohort at risk would raise the lower bound for mesotheliomas for 1976 to at least 10,000 to 12,000, using analogous calculations.

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 WWII. If the WWII shipyard workers had experienced the increased risk of the heavily exposed cohorts cited in the document, the WWII 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 HEW report from another point of view, if the WWII 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 HEW Report has ignored the spectrum of exposures to asbestos, which, when considered with established dose-response, readily show that the speculations are at least an order of magnitude too high.

An additional calculation, using the numbers and logic of the HEW report, for lung cancer deaths will also illustrate the lack of rigor. Using age-sex specific white death rates for 1976, Table 3 showed 131,866 deaths. If the WWII non-shipyard asbestos-exposed workers are considered, this figure would be raised to almost 190,000 deaths among WWII workers who experienced occupational asbestos exposures. If the increase in total deaths from the heavily exposed asbestos cohorts cited in the HEW report is then applied, this figure should be increased by approximately 40%, giving over 260,000 deaths among WWII shipyard and non-shipyard workers who experienced occupational asbestos exposures. Twenty-five percent of these deaths is almost 66,000 lung cancer deaths in 1976 from the WWII cohort alone. There were a total of 77,000 deaths in the entire U.S. coded to malignant neoplasms of the respiratory system (ICD codes 160-163: Table 1-13, Vital Statistics of the United States, 1972, Vol. II, Part A, HEW). Therefore, it follows that 87% of all respiratory cancer deaths in 1976 were due to asbestos exposure during WWII. The development used in HEW report actually predicts not future deaths, but past deaths, at an obviously unsupportable level.

There are several important recent studies not discussed in the HEW 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 and 1972 - 1973 (HEW, NIOSH publications 74-112 and 78-152) both reported:

"Ship components 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.)

A recent article in the Lancet (May 13, 1978) reported on a proportional mortality study of former Portsmouth Naval Shipyard workers. The control group (non-nuclear workers) revealed:

"Among non-nuclear workers, there was no statistically significant increase in proportional mortality from either leukemia or from all cancers." The control group from that study should be part of the shipyard worker cohort in the document. While no conclusion can be drawn, it is obvious that these data are not consistent with the HEW report.

There are other prospective and retrospective-prospective mortality studies in the literature dealing with identified asbestos-exposed cohorts.

This discussion has illustrated the lack of rigor of the speculations in the HEW statement by taking the logic and numbers put forth in the document itself. Looked at in this manner, the HEW report refutes itself. There are other approaches that should and will be pursued to put the entire matter into proper perspective.

Inappropriate Conclusions in Appendix A of the HEW Report

Appendix A of the HEW document states:

"The purpose of this Appendix is to show that the assumption of constancy of relative risk has a reasonable basis. Both relevant epidemiological data and the predictions of mathematical models of carcinogenesis will be considered."

Furthermore it states:

"Assumption of a constant relative risk would appear to be conservative, (Selikoff & Hammond, 1978; Peto, et al, 1977; Newhouse and Barry, 1976; Knox, et al, 1968)."

The final paragraph of the document states:

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

Consider first the assertion that a constant relative risk is reasonable or perhaps even conservative. No empirical data are given to support the conclusion. Table 6 for this critique has been derived from Table 4 in Selikoff and Hammond, 1978 (cited in Appendix A). The data in Table 4 of Selikoff and Hammond, 1978, describe the mortality experience of the cohort of 17,800 Asbestos Insulation workers, the largest cohort reported in the asbestos literature to date. A complete

discussion of the distinction between the relative risks used in Appendix A and SMR's (Standard Mortality Ratios) is not appropriate here. It is sufficient to note that the assumption of a constant relative risk would basically result in the long-latency SMR's to be constant. The decreasing lung cancer SMR's for the longer duration from onset of exposure categories supports a decreasing relative risk for older ages, not a constant relative risk. (The SMR divided by 100 is often used to approximate the relative risk.) Therefore, the data from the largest asbestos cohort in the literature are not consistent with the assumption of a constant relative risk, and certainly not with the suggestion that it would be a conservative assumption.

The HEW report appears to discuss "constant relative risks" in two contexts:

1. The first context is the extension beyond the latency period which would "usually" be covered in occupational mortality studies. (The empirical data presented in Table 1 are in conflict with that contention.
2. The second application of the "constant relative risks" in the HEW report is that any exposure to a carcinogen "results in a constant multiplicative increase in risk at all ages."

Consider now the treatment of that second point:

The multistage models discussed in Appendix A predict incidence rates at time t to be of the general form bt^k or $b(t-w)^k$, where b and w are constants and $t-w$ represents the "effective exposure" between first exposure and the first appearance of cancer as a pathological entity. (Taking w equal to the age at first exposure is a special case.) The relative risk is the ratio of the incidence rate of the disease of interest in the exposed population divided by the incidence rate of that disease in a control population. In the background (control) rate, t or $t-w$ ($t > w$) represent the latency period from the onset of all those endogenous or exogenous factors which account for the backgrounds. Thus, background rates, which will be the denominator in the calculation of the relative risk, have a time reference from either birth or the onset of exposure of those factors influencing the background rate. The numerator for the relative risk calculation involves the background rate plus the incidence rate attributable to the exogenous factors (i.e. the exposure) under consideration. It is a reasonable assumption that those endogenous and exogenous factors accounting for the background incidence will have been in effect at least as long as the exposure of interest. For example, if an endogenous factor is present since birth, then that time frame would be in effect long before the occupational carcinogen came into consideration; or a smoker who began at age 15 to 20 has that time frame in effect before the occupational exposure, if the occupational exposure begins at age 25, 30, or later. The quantitative result will differ depending on the assumptions of the multistage model, but figure 2A in the Appendix is misleading in any event. An example will illustrate:

$$t_1 = 20$$

$$t_2 = 30$$

$$t = 70$$

$$k = 5$$

$$R(70) = 1 + C (.154)$$

$$t_1 = 20$$

$$t_2 = 70$$

$$t = 70$$

$$k = 5$$

$$R(70) = 1 + C (.260)$$

If the description on Figure 2A is correct, $1 + C (.154)$ is compared with $1 + C (.260)$, not $(.154)$ with $(.260)$. (The value of C was not given.) Several observations are appropriate:

- It is true that the mathematical model, as it was used in the Appendix, will predict essentially the same relative risk for a range of values of t_1 and t_2 , if t_2 is much larger than t_1 (i.e. if the employee worked for a number of years).
- However, that model does not predict "approximate constancy of the relative risk" when t_2 is close to t_1 (i.e. a short exposure.) For example, $t_1 = 20$, $t_2 = 21$, $t = 70$, $k = 5$ will give $R(70) = 1 + C (0.020)$. Thus, even the model predicts much lower attributable risk for short exposures.

- 1 -
- Keeping in mind that this discussion involves a model, not empirical evidence, the dose is a part of that model. Lower doses model to lower risks.
 - The use of t_1 and t_2 in the Appendix of the HEW report is a special case of a multistage model and the use of "w" mentioned earlier.
 - In any event, the multistage model/relative risk discussion does not support the treatment of the WWII shipyard workers and all past occupational exposures in the report. The model supports "low" risks for short exposures and "low" risks for low exposures.

The discussion of the penultimate stage on page A-5 is not clear, since assumptions leading to the expression are not given.

The asbestos projections in the HEW report were done using proportionate mortalities, not life table/relative risk calculations. Even though Appendix A has not justified extrapolation and/or application of relative risks from heavily exposed cohorts to all exposed cohorts, it is instructive to see if the incorrect constant relative risk "conclusion" of the Appendix justifies the proportionate mortality treatment in the report.

Table 7 gives 1972 U.S. white male age specific death rates for all causes and respiratory cancer. Suppose a 65-69 age group

experienced the same death rate for all causes except respiratory cancer, which was 3 1/2 times the U.S. rate (i.e. a rate of $(3.5)(337.9) = 1182.65/100,000$). If $P_1 = 3927.4$ is the all cause rate for the U.S. population for white males, $P_2 = 337.9$ is the respiratory cancer rate and $R = 3.5$ is the relative risk for lung cancer, then the percent of total deaths for the hypothetical 65-69 age group will be $100(R \cdot P_2) / (P_1 + (R-1)P_2) = 24.7\%$. If we leave $R = 3.5$ constant and perform the same calculation for the higher age groups, we get:

<u>White Males</u>	
<u>Age Group</u>	<u>% Respiratory Cancer Deaths for Constant R=3.5</u>
65-69	24.7%
70-74	20.6%
75-79	15.2%
80-84	9.4%
85+	4.4%

Therefore, even if the constant relative risk were applicable, the constant proportionate mortality rate is not correct. Other causes of death (i.e. competing causes of death) play a larger role in the older age groups.

The report also did not consider sex-specific death rates. The unsupportable proportionate mortality from heavily exposed male cohorts was applied to females also (they were a definite part of the WWII and subsequent workforce). The carelessness of the calculations are illustrated by applying a constant relative

risk of 3.5 to the white female rates in Table 8, just as was done for the white male rates in Table 7.

<u>White Females</u>	
<u>Age Group</u>	<u>% Respiratory Cancer Deaths for Constant R=3.5</u>
65-69	9.5%
70-74	6.4%
75-79	3.7%
80-84	2.6%
85+	1.3%

The above calculations illustrate that if the calculations in the HEW report have been made as claimed in the report (even though they were not supportable), the proportionate mortality argument used is invalid because of: 1) competing risks in older ages, and 2) sex-specific rate differences. (Female lung cancer rates are increasing, but they are still much lower than male rates.)

Therefore, it has been shown that epidemiological data and the predictions of mathematical models do not support the predictions of the HEW report.

TABLE 6

Adapted from Table 4 from Selikoff and Hammond, 1978

<u>Duration from Onset of Exposure</u>	<u>Lung Cancer SMR*</u>
<10	0
10 - 14	253
15 - 19	338
20 - 24	346
25 - 29	494
30 - 34	606
35 - 39	575
40 - 44	480
45+	387

*Standardized Mortality Ratio: 100 (Observed/Expected)

TABLE 7.

U.S. White Male Annual Death Rates/100,000 - 1972

<u>Age Group</u>	<u>All Causes</u>	<u>ICD 160-163*</u>
50 - 54	1056.7	90.7
55 - 59	1721.8	163.3
60 - 64	2669.8	248.6
65 - 69	3927.4	337.9
70 - 74	5896.6	407.3
75 - 79	8851.6	431.9
80 - 84	12592.9	361.2
85+	20266.2	260.4

*Malignant Neoplasms of Respiratory System

TABLE 8

U.S. White Female Annual Death Rates/100,000 - 1972

<u>Age Group</u>	<u>All Causes</u>	<u>ICD 160-163*</u>
50 - 54	526.8	32.6
55 - 59	819.4	45.2
60 - 64	1202.8	48.7
65 - 69	1876.0	54.5
70 - 74	3100.5	59.2
75 - 79	5325.0	57.9
80 - 84	8588.9	64.7
85+	16657.3	64.5

*Malignant Neoplasms of Respiratory System

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Comments on the Discussion of the Document Entitled, "Estimates of the Fraction of Cancer in the United States Related to Occupational Cancer," Held September 26, 1978 at the Sheraton International Conference Center, Reston Virginia

The purpose of the following excerpts from the conference I attended is primarily to emphasize the limitations and the unsupportable projections made in the NCI/NIEHS/NIOSH document, as viewed by a significant percentage of the scientists invited by the Director of the National Cancer Institute to a conference on the quantitative aspects of cancer prevention. A listing of the participants is available from the Director, NCI.

If a transcription of the discussion in the session alluded to above has been entered into the record, the excerpts contained in this response are superfluous. However, I have no knowledge that a transcript has been made and submitted for the record. The quotes are all to a degree "out of context," and I recommend that the Assistant Secretary for Occupational Safety and Health make every effort to review the transcript.

The discussion was chaired by Dr. Peter Greenwald, Director, Division of Epidemiology, New York State Department of Health.

Dr. Umberto Saffiotti, of NIH, NCI, noted in his comments:

"In the last few weeks, I forget exact dates now, Dr. Rall, I believe, discussed this point with Secretary Califano who made a reference to this draft in his address to the AFL-CIO meeting two weeks ago, and also I think there was a certain desire to bring at least the sort of first writing

of this material to a reasonable stage where we could feel comfortable with submitting it as part of the record to the Occupational Safety and Health hearing record on occupational carcinogens. This is a record that OSHA has been building over many months with contributions from a large number of people from all sides of our society including oral testimony that is transcribed and written statements. Essentially, it is a discussion record of points that are brought to the attention of the agencies for their consideration. So, in that context, this document was submitted to the record. It is the intention of the group of people who have worked towards this document to now go back to it and try and work on it further to prepare it for publication in the scientific literature. So, it is not a published paper in this common sense of being ready for publication in the scientific journal. We intend to work on it to eventually submit it to a journal for review and publication, but I think it is an important attempt to bring up some of the key issues that were addressed here and in that respect we felt that it was important to put that in the public record at this time."

Dr. Greenwald in his response noted:

"My first impression is that there are no authors; there is a list of nine contributors in alphabetical order, but there is not one that is very competitory and one contributor to the Appendix. I was hoping to have someone who was willing to strongly defend the conference."

Dr. Greenwald further noted:

"Much of the prediction is derived from the asbestos situation, and on page 9 it says that there were 4 million people heavily exposed to asbestos. This, and I'm confused because on Table 1 on page 30, it seems to say 1.6 million rather than 4 million; and it says of these exposed 20-25% over their lifetime will get lung cancer. Seven to ten percent will get mesothelioma. That turns out to be about 300,000. Now, as an example, in upstate New York, in the history of our registry which is about 30 years, we have about 200 cases, so it is a substantial increase. That 8-9% will get GI cancers, and in general, 13-18% of the estimate of the 20% estimate is based on asbestos. Then, it lists a number of other carcinogens giving very large numbers of exposed in the United States, 1.5 million to arsenic; 1.4 million, cadmium; 1.5 million, chromium; 2.2 million, vinyl chloride. I thought there was a distinction between polyvinyl chloride, but there isn't; and I couldn't get a clear picture. I assume that you mean clearly exposed, not a secretary in the industry; and so I guess I am a little biased, but the impression is that this is derived

from some rather crude estimates of the number of people in the industry, then pointing to one or several studies estimating relative risks, translating this to life-long risks where this number was exposed and then shifting back to annual number of cases and coming up with 20% as a conservative estimate."

In response to a request to comment, Dr. E. Cuyler Hammond, American Cancer Society, who has worked with and coauthored with Dr. Selikoff virtually all of the publications that were used as references in the NCI/NIEHS/NIOSH document, stated:

"Well, if you are taking a very large number, the largest number -- well no, I think we're speaking only of occupational exposure. This document, as I understood it, unless it's changed in a later draft, says that about exposure, so I'm speaking of that point. The biggest single number of people who have been occupationally exposed to asbestos were people who were in shipyards during the shipbuilding program which started some few years before the United States got into WWII. Our first real worry about those people came from experience in England, felt back where they started earlier they started seeing mesotheliomas associated with that exposure. Now, this was a very large number of people in the United States, I forget the exact figure, but first you have to remember that a considerable portion of them have died so they are not exposed to the risk of dying of cancer from here on. Now, as far as American shipyards are concerned, we have information on members of asbestos workers union. The pipe coverers, in England they call them ladders, primary installation working shifts, because there are several locals of that international union that did virtually all that work in the shifts during WWII period, and we have the records on all of them. Now, you cannot use those figures to extrapolate to the rest of the people for this reason. Almost all those men continued as asbestos workers years before the war, a few came in as young men then, and they continued to be asbestos workers for a great many years thereafter. So you are dealing with a much longer duration and exposure than the person who works in the shipyards from a few weeks to a few months to two or three years, and then was not further exposed. I believe the experience that people such as I am speaking of, that is, regular asbestos workers who worked on that, my impression was that the first draft of this document, this is where the basis of it in saying how many people were exposed. However, this is a very small number exposed in that way and continued to be exposed, a very small number indeed. Now, as to the others, I cannot give documentary proof of it. Herb Seidman and I have analyzed

it upsidedown and backwards and forwards. Our impression is as follows.

"For short-term, even rather heavy exposure to asbestos, and even in the cigarette smoker, 20, 30, 40 years later, they haven't died. Their death rate from lung cancer probably will not be greatly increased. The probability is that the big increase will be mesothelioma, not lung cancer. Since lung cancer is the bulk of it, mesothelioma's part is a smaller proportion. Now, therefore, this has to be taken into consideration when you try to extrapolate. We have, really, no information as to the age distribution, duration of exposure and extent of exposure of any of these people, except those who are actually working as installation workers. We don't have it. We don't know how many have already died. I'm speaking of the shipyard workers, by the way. Knowing Irving Selikoff and I published a paper in CA several months ago, and the purpose of it was we knew the Secretary was going to put out a statement on the shipyard workers and we wanted to call physicians' attention to it in areas where these people lived so that they can look out for it and signs and symptoms and hopefully maybe being able to do something about it. When we sent it in, we gave no estimates of how big this problem was and the editor complained. He said, 'well is this a big problem or a little problem?' I said, 'I am so sorry, but I don't know because we don't have the data on which to base it.' Well, he said, 'I want some statement on it.' So, Irving and I got up this statement, I think I can quote it almost exactly. We said that we had no American experience on this and we don't know. We had some English experience, a little European experience, I think we had one Japanese report on it, I'm not sure. Based upon that, we are quite certain that we are going to begin to see it in America, and we have a few cases already. As to numbers, we said on mesothelioma we are quite certain that there will be a few hundred deaths among the people from mesothelioma. There may perhaps be many thousands, we hope not. And that was as close as we could come to making any estimate of it at all, and I think we probably have more data than anybody on which to base it. I mean our own and all the rest of it. We spent weeks going over this to try to get something. Now, for all these other exposures, how you got up to 11 million, I am slightly puzzled. One of the biggest groups that has had intermittent exposure are not labeled as asbestos workers at all. When asbestos is being sprayed on pipes or being put up in insulating ceiling areas, the asbestos drops to the floor, and this is swept up usually with brooms rather than a vacuum cleaner by a member of the laborers union. In general, almost no precaution is taken on that. The industry has no control over it, I mean the asbestos industry, and the asbestos union has no control over it. Now, we have observed cases where they just raised clouds of dust and they must have quite heavy exposure intermittent because this is the only job they do."

Dr. Richard Peto, Reader in Cancer Studies, Radcliffe Infirmary commented as follows:

"In this report, the estimated number of asbestos-related deaths based on the data, which Dr. Hammond has been the chief epidemiologist analyzing, is 2 million. His estimates of the number is more like 2,000 than 2 million. He, therefore, makes it 20,000. This report appears to be at variance with his judgement by a factor of at least 100, possibly a thousand. It has been obtained by a kind of race for the asbestos insulators to a very large population (a population of 4 million who are said to have been employed in the asbestos industry). They are all being treated as though they had been asbestos insulators for years. It's comical. Do you accept my comments? This is ..."

Following my recognition by the Chair, I identified myself and the corporation for which I work. I further observed:

"Obviously, I am not going to discuss data in the presence of Dr. Hammond, since the data that he and Dr. Selikoff have provided in the community essentially speak for themselves. And let me begin with my last topic. First, I'm sure Dr. Higginson would be dismayed to learn that in any pronouncement he makes as the Director of the International Organization of Research Against Cancer, he might be accused of being unaware of multi-factorial etiology. I certainly think he is one of the more potent contributors in terms of this general body of knowledge.

"I know Dr. Saffiotti is enough of a scientist so that he shares many of these concerns that he has alluded to and would be happier with, not the absence of, such a document, because I think there's a legitimate right and need for such a document, but one that more nearly relates to the high quality of his previous papers. I'm further a little intrigued by the fact that the first page of the document says that they want to know what is the best estimate -- the statement addresses the question of what is the best estimate of the fraction of cancer incidence or death in the United States that is reasonable to attribute to occupational exposure in the present and the foreseeable future. I looked for the word "attribute" on the front and couldn't find it. It's not important, but I think it indicates some degree of questioning within the minds of the others.

"In looking for reasons why they, the authors, could not identify any impact of asbestos cancer morbidity and mortality in the general population, they listed three or four possible explanations, all of them clearly defensible and logical, but I think the tone of the document is clear in

the sense that it might have occurred to one of them that may be exposure was a no-effect level or threshold level. We know that people are exposed to carcinogens and do not have evidence of the impact on morbidity or mortality."

My final reference refers to Dr. Norton Nelson, Professor and Chairman, Department of Environmental Medicine, New York University Medical Center:

"This will be like making a very brief comment. I think that what Dr. Hammond has reviewed for us here is very fundamental and I do hope that he will be willing to have the recording touched up, if he wishes by himself and made available. It can be a very useful analysis. On a minor personal note, I am slightly distressed to see that my name is mentioned, and I suppose it serves me right having participated in what was really a very silly enterprise which, in fact, I was at the time. What I'm puzzled about is that it really doesn't conform with what I was generally saying in fact. I have a manuscript here which is something I have been saying for a good many years is that I put probably more than 5%, probably less than 15%, somewhere between. In any event, what I'm more deeply concerned about than that rather trivial issue is that we have a statement such as Cuyler has just made. I'm deeply concerned that a statement which is going to fall apart and cannot be adequately supportable will, in effect, damage the enterprise which so many of us are concerned with. I guess no one here would say that I am trying to give a lower estimate of occupationally related cancer. I think there's a great danger in using a federal document of this sort which may fall apart."

In closing, let me restate my awareness that the quotes of necessity are excerpted from a combination of memory and an informal transcript of the discussion. The limitations inherent in "excerpts" are evident, and I would hope they would provide an impetus for reference to the total transcript.