

Rutgers-Dickinson University

RUTHERFORD TEANECK MADISON

March 1977

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PLAINTIFF'S
EXHIBIT
WRG-728a

This responds to your letter of the 18th in which you ask for comment on a NIOSH report of December 1976 that recommends a revision of the asbestos standard to 0.1 fibers per cc.

As I read this document, it does not present evidence for hazard from either a 5 fiber or 2 fiber per cc standard. Essentially, it argues that risks from low level exposures to asbestos are indicated by reports of mesotheliomas associated with brief or with non-occupational exposures, such as "household" exposures of persons living in the houses of asbestos workers, but levels of such exposures are not stated. That "household" exposures have been substantial was indicated by Dr. Selikoff at a Conference on Environmental Cancer that I attended in Washington last week.

The NIOSH report mentions mesotheliomas in individuals with history of asbestos exposure for only one day. Such cases could, of course, be unrelated to asbestos, as indicated in the NIOSH statement (Page III-7) that approximately 15 per cent of mesotheliomas are not known to be related to exposure to asbestos.

An earlier NIOSH report (Gillam et al) has been cited as showing tumor response to low levels of asbestos. In referring to this, the 1976 NIOSH report (III-10) states: "In a study of a group of miners exposed to amphibole fibers in the cummingtonite-grunerite ore series, Gillam et al (1976) have demonstrated mortality from malignant respiratory disease three times that of the general population."

Referring to the same study, a 1975 OSHA report said: "Gillam et al (1975), studying the mortality and reviewing the chest x-rays of 439 underground metal miners exposed to an asbestiform mineral, found three times the risk of malignant respiratory disease than expected. The fiber concentrations averaged 0.24 fibers/ml." (Federal Register, Oct. 9, 1975 pages 47652-47665. Refer to page 47656).

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The claim by Gillam et al for an increased incidence of cancer in the cited miners has not been born out by a more extensive study by McDonald et al (copy attached).

You no doubt have a copy of the above cited 1975 OSHA document. On an enclosed copy of it, I have marked paragraphs that attempt to quantitate exposures to asbestos in relation to occurrence of asbestosis and/or cancer. It should be noted that the level of exposure in the cited British factory in the period 1933-1968 was an estimated level and that no evidence is offered that a 2 fiber level had actually been achieved in the period after 1968.

The 1976 NIOSH report (II-7, II-Table 6) cites a study by Wagner on inhalation exposures of rats to various preparations of asbestos and notes that tumors were found after exposures of only one day. A copy of Wagner's paper is attached. It states that the one-day exposure was 7 hours exposure to dusts containing 9.7 to 14.7 mg per cubic meter of the tested preparations of asbestos.

In March 1976, NIEHS held a 3-day Conference on Extrapolation of Data from Animals to Man. A report on that conference by its chairman is enclosed. I attended that conference and enclose copies of 3 papers that seem of particular pertinence.

The first is a paper by Rall (Director, NIEHS) which addresses the question of threshold levels for carcinogens.

The second is a paper by Enterline and Henderson "A Model for Extrapolating to Low Levels of Asbestos Exposure."

The third is by Hardin Jones. He brings out the point that thresholds for carcinogens should be viewed not only in terms of yield of tumors but also latent period, i.e. that safe levels can be achieved by considering exposures with latent periods longer than the life span.

I understand that CONSAD Research Corp., contractor for inflationary impact study on proposed revision to asbestos standard, is also looking at technical feasibility and economic implications of a 0.1 fiber per cc limit.

Trusting that these remarks may be of interest,

Very sincerely,

William E. Smith
William E. Smith, M.D.
Director
Health Research Institute

WES/elc

Enclosures

See addendum (page 3)

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Addendum

The enclosed papers from the NIEHS Conference on Extrapolation of Data from Animals to Man are offered merely to provide detail on some current thinking on that subject.

Perhaps a "bottom-line" attitude that seems to be developing in the regulatory agencies was expressed last week by Rula Bingham at the conference I covered in Washington. Dr. Bingham, the new Asst. Secretary of Labor for Occupational Safety and Health, said, according to my notes, "We are ignorant as to whether there is a safe level for carcinogens. The lowest feasible level seems to be the prudent path."

On this theme, the NIOSH document that you sent me contains a statement on page VI-2 that the asbestos standard "should be set at the lowest level detectable by available analytical techniques, an approach consistent with NIOSH's most recent recommendations for other carcinogens."

This approach, or enactment of "zero" levels for carcinogens, would, of course, mean that investment of time and money to achieve any particular level would be precarious, since improvements in sensitivity of analytical techniques could unpredictably change the picture.

Enclosed is an announcement of a seminar in Washington on 12-13 April on Federal Regulation of Environmental Carcinogens. The list of speakers may suggest someone that you could contact for comment or advice. Paul Kotin from Johns-Manville is scheduled to give the lead-off address.

Would it be agreeable for me to send a copy of this letter to Dr. Allan Harvey at R.T. Vanderbilt Co. ?

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From the desk of
E. S. WOOD

To: A. S. Stocker

cc: J. Walter

Director

Please review this
and explain the log
assumptions and their
significance to me.

(Table 2) — i.e. which
ones are the most
sensitive ones controlling
the predicted cumulative
relative risk.

Can we make extrapol-
ations to 1.0, 0.5, and
0.2 $\mu\text{g}/\text{ml}$? *Chap 4/17/77*

Abstract

A Model for Extrapolating to Low Levels of Asbestos Exposure*

by

E. Enterline and V. Henderson
University of Pittsburgh

1987

A considerable amount of epidemiological data are available relating occupational asbestos exposure to respiratory cancer. Some recently published data provides the basis for developing a continuous exposure model and for extrapolating to low dose levels. These data, summarized in Table 1 are for a population of 7,800 U.S. asbestos insulators estimated to have had historic exposures of about 15 f/cc for half their working day or an 8 hour average of 7 1/2 f/cc.

A model was tested with assumptions as shown in Table 2. One of these, the estimate of median time to tumor, is based on Table 1 plus the assumption that the high intermittent exposures which characterize asbestos insulators are twice as effective in producing respiratory cancer as the steady exposure which characterize factory workers. Thus, the 7 1/2 f/cc integrated exposure over a 8 hour day for insulation workers is assumed to be equivalent to a 15 f/cc integrated exposure for factory workers.

As a first step in developing the model a simple linear dose-response relationship was assumed resulting from one year's occupational exposure to asbestos (8 hours a day, 5 days a week) and 40 cases were arbitrarily assigned to the lowest dose level (4 f/cc). Also, median time to tumor was assumed to be equal to the inverse cube root of dose with time to tumor for an exposure level of 16 f/cc estimated at 39.1 years based on Table 1. A log normal distribution was assumed for a single dose (one year's duration) with a geometric standard deviation of 1.5. The results for four exposure levels are shown in Figure 1.

Based on a study of a factory population with a very high exposure of short duration (estimated at 30 f/cc for 3-11 months) for which we estimate the actual cumulative relative risk for respiratory cancer at the end of 28 years was 2.9, an expected annual number of respiratory cancer deaths was calculated. To do this it was necessary to estimate the number of cases caused by 5/8 year exposure at 30 f/cc under conditions set forth in Table 3. This was estimated as 215 cases with a median latent period of 31.7 years. 81.3 of these cases would be observed in the first 28 years. Since the cumulative relative risk over a 28 year period corresponding to the 81.3 cases was known (2.9), expected case:

*Presented at Conference on Problems of Extrapolating the Results of Laboratory Animal Data to Men and Extrapolating the Results from High Dose Level Experiments to Low Dose Level Exposure, Pinehurst, North Carolina, March 11, 1976.

per year and a known number of cases caused by asbestos exposure per year for various exposure levels (Figure 1), relative risks for each year could be calculated for any exposure level. To illustrate, the calculation for 32 f/cc for a 40 year period is shown in Table 4. This represents a total of 295 cases of which 60 are due to cancer other than asbestos exposure and 235 are due to asbestos exposure. That is, 235 of the 320 cases shown in Table 2 must occur in the first 40 years after a single years exposure at 32 f/cc, given the distribution shown in Figure 1.

One other epidemiological study of a factory population is available to check on the estimate of a relative risk of 2.9 after 3-11 months exposure and this gives about the same result.

Tables 5 and 6 summarize results that would be anticipated under two study designs for populations exposed a single year. Table 6 shows that even a single year at a very high dose level (32 f/cc) would produce a high relative risk (2.5) if follow-up was not started until 20 years after first exposure and continued for 20 years. On the other hand, Table 5 shows that only a modest relative risk would be observed in the first 20 years (2.5).

Estimation of the effects of a single year of exposure is not of great interest. What we need to know is what might be observed as the result of continuous exposures at various levels. Table 1 suggests the need for an additional parameter - a parameter we'll call the Index of Susceptability. Table 1 shows that rather than continuing to increase as dose increases the relative risk for respiratory cancer starts to decline after 34 years of exposure. One explanation for this is that susceptibility varies in a population and with continued exposure the population loses its ability to respond. One expression of this is a function such that if one year's exposure at, for example, 15 f/cc causes 150 cases (estimated from Table 2) the 2nd year's exposure causes $150 \times c$ cases, the 3rd year $150 \times c^2$ cases, the 4th year $150 \times c^3$ cases, etc., where c is some constant < 1 . To determine the value of c , data in Table 1 were first adjusted for an overstatement of the relative risk due to the use of corrected death certificates for observed deaths among insulation workers and the use of uncorrected death certificates to obtain expected deaths. The model was then fitted to these corrected data for various values of c . The best fit was obtained where $c = .44$ (the Susceptability Index). This fit is shown in Table 7. It is pretty good considering that the insulation workers data deal with fairly small numbers in some of the exposure categories.

Given a Susceptability Index, estimates can be made of the effects of continuous exposures of various durations and at various dose levels. Table 8 illustrates the effects of continuous exposure at 32 f/cc and Table 9 and 10 the predicted results for two study designs for various exposure levels. Relative risks are rounded so that a relative risk of 1.0, for example, means less than a 5% increment in respiratory cancer. Also, distributions are discrete and somewhat more precise estimates could be obtained if continuous distributions were used.

Comparing Tables 9 and 10 with Tables 5 and 6 shows that the difference between the effects of a single years exposure and continuous exposure are not as large as might have been anticipated. This is due to the low Susceptability Index (.44). The relatively high response to very short exposures (as compared to long exposures) is consistent, however, with many epidemiological observations on asbestos.

Table 11 shows the effects of continuous exposures at four levels for 20, 40, and 60 years. The current threshold limit value for asbestos is 5 f/cc averaged over an 8 hour day, not to exceed 10 f/cc at any one time. As is true for most standards, no epidemiological data on factory workers exposed at this level are available. Table 11 shows that at 4 f/cc the model proposed here predicts a 20% increase in respiratory cancer among factory workers after 40 years and a 40% increase after 60 years.

One interesting feature of Table 11 is the decline in the cumulative relative risk at 4 f/cc continuous exposure at the end of 60 years. This is consistent with the declines shown in Tables 6 and 7 although it should be noted that these tables deal with relative risks in specified intervals rather than cumulative relative risks (see Tables 4 and 8). Cumulative relative risks would seem to be the best summation of the health effects of exposure, and can readily be translated into cases caused by exposure.

Table 1

Lung Cancer Observed During 1967-72
by Years from Onset of Exposure as of
January 1, 1967

17,800 Asbestos Insulation Workers

Years From Onset	Expected Deaths	Lung Cancer Observed Deaths	Relative Risk
<10	0.55	0	-----
10-14	1.97	5	2.5
15-19	5.87	23	3.9
20-24	9.55	34	3.6
25-29	10.70	56	5.2
30-34	8.20	60	7.3
35-39	4.68	29	6.2
40-44	4.84	27	5.6
45-49	4.51	19	4.2
50+	4.97	22	4.4

(Selikoff and Hammond, 1975)

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Table 2

**Major Assumptions
Dose Effect Model for Asbestos**

Assumption	Reference
Linear Dose-response Relationship between Asbestos and Respiratory Cancer	Enterline et al. McDonald et al.
Respiratory Cancer Log-normally Distributed SD = 1.5	Bliss et al. Lundin et al.
15 f/cc has Median Latent Period of 40 Years	Sellkoff et al.
Median Time to Tumor $t = t_0 \left(\frac{D_0}{D} \right)^{1/3}$ where $t_0 = 40$ $D_0 = 15$	Jones et al. (and others)
For 3-11 mos. Factory Exposure Prior to 1945 RR = 2.0 for 25 years	Sellkoff et al. Newhouse et al.
Factory Exposure Prior to 1945 = 30 f/cc	Various Sources
Intermittant Exposure has Double Effect of Continuous Exposure of Same Dose	Enterline et al. OSHA Standard
male:ft. Susceptability Index = .44	Derived from Model

Table 3

**Total Cases Caused by Exposure for One Year and
Median Latent Period**

Exposure Level (f/cc)	No. of Cases	Median Latent Period
4	40	62.1
8	80	49.3
16	160	39.1
32	320	31.1

Table 4

**Observed and Expected Cases and Relative Risks
32 f/cc for One Year (1954)**

Follow-up Period	Observed Cases	Expected Cases	RR in Period Obs/Exp	Cumulative RR at end of Period
1955-59	8	7.5	1.1	1.1
1960-64	8	7.5	1.1	1.1
1965-69	18	7.5	2.4	1.5
1970-74	40	7.5	5.3	2.5
1975-79	58	7.5	7.7	3.5
1980-84	62	7.5	8.3	4.3
1985-89	56	7.5	7.5	4.8
1990-94	45	7.5	6.0	4.9

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Observed and Expected Cases Caused by Exposure for One Year (1954)
First 20 Years of Follow-up

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Mean Exposure Level (f/cc)	Observed Cases (1955-74)	Expected Cases (1955-74)	Cumulative RR End of 1974
4	30	30	1.0
8	31	30	1.0
16	38	30	1.3
32	74	30	2.5

Table 6

Observed and Expected Cases Caused by Exposure for One Year (1954)
Second 20 Years of Follow-up
(Follow-up Starts 20 Years After First Years of Exposure)

Mean Exposure Level (f/cc)	Observed Cases (1975-94)	Expected Cases (1975-94)	Cumulative RR End of 1994
4	35	30	1.2
8	53	30	1.8
16	105	30	3.5
32	220	30	7.3

Table 7

Relative Risk Predicted by Continuous Exposure
Model at 15 f/cc Compared with Relative Risk
Reported in Study of U. S. Insulation Workers

Years from Onset of Exposure	Predicted Relative Risk	Observed Relative Risk (Adjusted)
<10	1.0	0.0
10-14	1.6	2.2
15-19	2.8	3.4
20-24	4.3	3.1
25-29	5.4	4.5
30-34	5.7	6.4
35-39	5.4	5.4
40-44	4.8	4.9
45-49	4.1	3.6
50+	3.4	3.8

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Observed and Expected Cases and Relative Risks
Continuous Exposure at 32 f/cc Starting in 1954

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Follow-up Period	Observed Cases	Expected Cases	RR in Period Obs/Exp	Cumulative RR at End of Period
1955-59	8	7.5	1.1	1.1
1960-64	9	7.5	1.2	1.1
1965-69	23	7.5	3.1	1.8
1970-74	59	7.5	7.9	3.3
1975-79	93	7.5	12.4	5.1
1980-84	104	7.5	13.9	6.6
1985-89	95	7.5	12.7	7.4
1990-94	78	7.5	10.4	7.8

Table 9

Observed and Expected Cases Caused by Continuous Exposure
First 20 Years of Follow-up

Mean Exposure Level (f/cc)	Observed Cases (1955-74)	Expected Cases (1955-74)	Cumulative RR End of 1974
4	30	30	1.0
8	32	30	1.1
16	42	30	1.4
32	98	30	3.3

Table 10

Observed and Expected Cases Caused by Continuous Exposure
Second 20 Years of Follow-up
(Follow-up Starts 20 Years After First Year of Exposure)

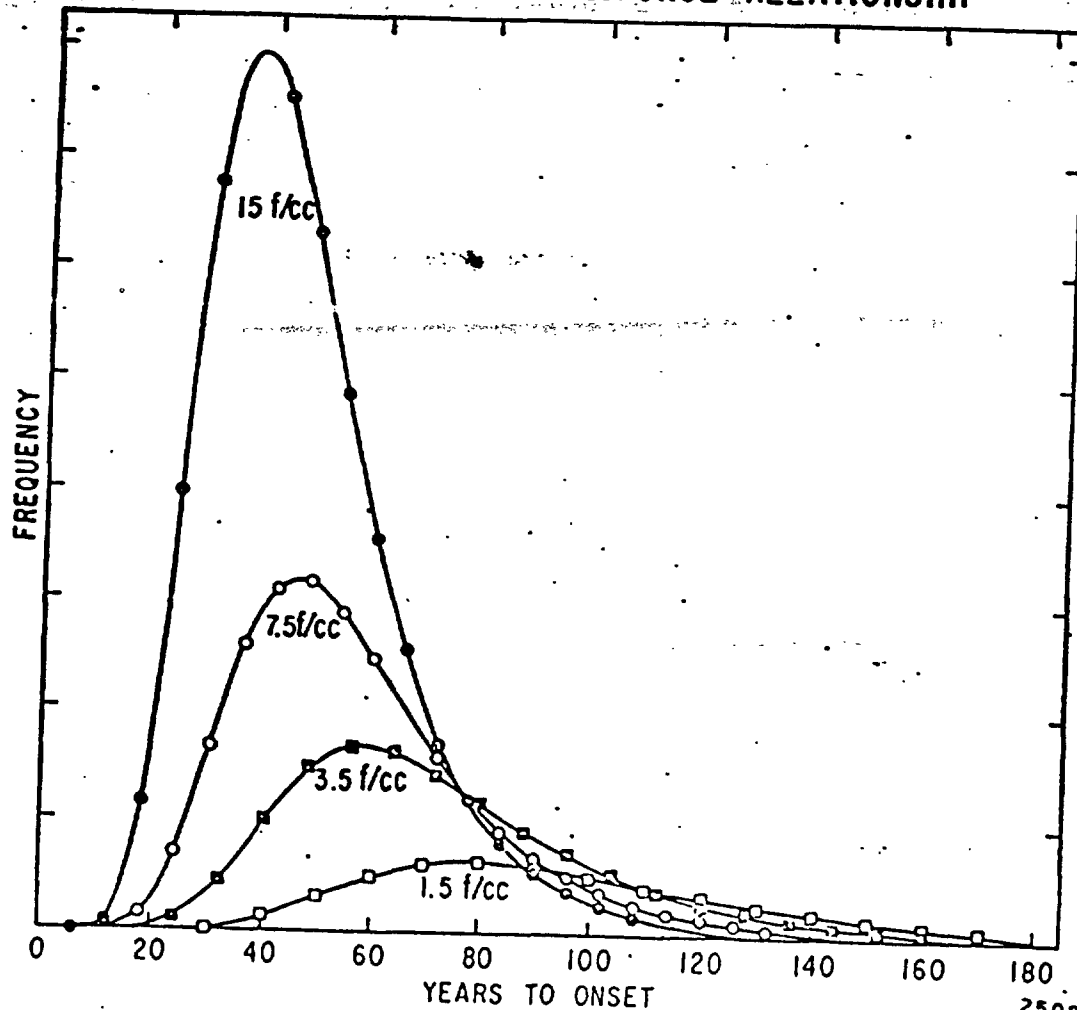
Mean Exposure Level (f/cc)	Observed Cases (1975-94)	Expected Cases (1975-94)	Cumulative RR End of 1994
4	39	30	1.3
8	69	30	2.3
16	161	30	5.4
32	371	30	12.4

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20 Year, 40 Year and 60 Year Cumulative Relative Risks
at Four Levels of Continuous Exposure

Exposure Level (f/cc)	20 Year	40 Year	60 Year
4	1.0	1.2	1.4
8	1.1	1.7	2.1
16	1.4	3.4	3.7
32	3.3	7.8	7.0

RESPIRATORY CANCER AT FOUR INTENSITY LEVELS
FOR A LINEAR DOSE RESPONSE RELATIONSHIP



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