cc: B. Williams 7/22/77

GRACE

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Date: March 28, 1977

From: R. H. Locke

Subject: Dose:Response Relationship in Occupational Asbestos Exposure

cc: W. F. McCord

On September 13, 1976 I referred to Professor Philip E. Enterline's original work in this subject area in a report on the 1976 Agency-Industry Conference on Asbestos. Several people subsequently asked me what Enterline's statistics meant. Accordingly, I am bringing to your attention the attached full text of his remarks at the Conference of September 8, 1976.

As you will note from the attachment, his model's results are directly related to the question of whether a lower occupational exposure standard is (1) indicated and (2) would have an employee health dividend. As you are aware, this is a point both OSHA and NIOSH have finessed in their proposals for 0.5 f/ml and 0.1 f/ml standards.

In a nutshell, Enterline projects that the current standard reduces relative risk of death due to mesothelioma and all forms of lung cancer to a comparatively low level. You will note, however, that some positive response is (naturally) associated even with very low exposure, although he has little data to check with in that area. His response curves are based upon all significant epidemiological studies of commercial asbestos published to date (primarily chrysotile), including those of researchers such as Selikoff. Enterline is with the University of Pittsburgh (as is Morton Corn). He is Chairman of the Department of Biostatistics.

Enterline told me last Friday that he has just received a notice of manuscript acceptance from the Archives of Environmental Health for his final draft in this subject, and publication is expected in 90 days. I am attaching his whole talk, although he gets into modeling only commencing with p. 180. The article when published will deal with that topic.

R. H. Locke

R. H. Locke

RHL/cf
Attachment

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Remarks of Philip E. Enterline, Ph.D.
Professor of Biostatistics, Graduate School of Public Health
University of Pittsburgh

at

Asbestos Information Association
Third Annual Industry-Government Conference

September 8-9, 1976

Dr. Enterline is Professor of Biostatistics, Graduate School of Public Health, University of Pittsburgh. He received his undergraduate education at Westminster College, and his postgraduate degrees at the American University.

Dr. Enterline is a recognized expert in the fields of biostatistics and industrial epidemiology. He has published a number of distinguished papers. Prior to joining the Univeristy of Pittsburgh faculty, Dr. Enterline served in a variety of responsible positions in the U.S. Public Health Service. He has a broad background of experience on health advisory committees and has done extensive consulting work for government, academia and private industry.

Listening to Alex Cross reminded me of a grand tour I did of England back in 1962 when I first got in the "asbestos business." I'll never forget a young statistician who was assigned to orient a group of us about the problem in England and what was going on, and throughout his entire presentation he talked about the "asbestosis" factories in England. The man next to me said, "Oh, how I wish we could get him to stop saying that!"

I was asked today to talk about a project I've been doing for the Asbestos Information Association, and I'll spend a little bit of time talking about it, not much time, because I haven't gotten into it very deeply. This is something Guy Gabrielson asked me if I would undertake and is being done with the help of one of my graduate students. The question we're trying to answer is, "What did we know about the association between asbestos and cancer at various points in time as we go back through history? What did the experts think about the assosiation in 1935, 1940, 1945, etc.? At any point in time what was the expert opinion? What did writers think about what they were seeing?"

This is an interesting kind of project because it requires doing something that to my knowledge has never been done. It means reading not only the summaries of the various articles, but the introductions and the discussions, and if it's a paper given at a meeting, the discussions of the paper from the floor and the questions and answers, if they're published. Also, all the editorials that have been written about asbestos and cancer, textbooks, letters to the editor, and questions and answers in the leading medical journals. Then try to form some kind of opinion about what was believed at these various points in time.

The game plan is that we'll have one or two graduate students do the actual screening of the literature (photographing the pages that are relevant) and then have a biostatistician and an epidemiologist independently review this material and make some decisions about what points in time were certain things known. I want to emphasize that we're not trying to find out when should we have known; we're trying to find out when did we know. When did the writers of the various periods realize what they were dealing with? That's something a little different than an ordinary literature review.

To give you a sampling of what we find when we do this, I'll show you a couple of things we've abstracted which illustrate a number of points about this particular project.

The first slide is a writing from the bulletin of the American Society for the Control of Cancer and was written in 1943. I'm going to talk only about asbestos and lung cancer in order to narrow this thing down somewhat.

Slide #1

1943
Bull. Am. Soc. Cont. of Cancer

> "Asbestosis cancer of the lung is the most recent newcomer among the occupational cancers of this organ. First described in 1935, there are now 18 cases of this industrial cancer on record observed among asbestos workers in England, Germany, and the United States. The latter contributed five cases. Inasmuch as the asbestos industry is most extensively developed in this country asbestosis cancer of the lung has for us a special hygienic and sociologic significance.

Now this is interesting because it's based upon reports on an association of asbestosis and bronchogenic carcinoma at autopsy, and it is written by Bill Heuper whom some of you surely know. He wrote a great deal about occupational cancer. Now let me show you a writing in 1961. This slide is from the Journal of the American Medical Association. That's a very prestigious journal, and this writing is even more prestigious because this happens

to come from a section of that journal that answers questions that are asked by the medical profession. If you're a practicing physician and want the latest information on a particular topic, you write to the Journal. They refer your letter to someone they consider a leading expert and that person will then reply in the columns of the journal to your question.

Slide #2

> "There is no epidemiological evidence that silicosis, resulting from undue exposure to free silica, produces cancer of the lung. Of the several silicates, asbestos is held in suspicion, especially in Great Britain. In the American literature there is no evidence that there is a relationship between asbestosis and lung cancer. The reason for the difference between the English and American experience is not apparent. It may be due to a difference in the type of asbestos fiber or to the total dosage."

As you might expect, in 1961 there was considerable correspondence which followed this, however, the writer stuck to his opinion and defended it on the grounds that there was no epidemiologic evidence and points out in subsequent commentary in the Journal that without epidemiologic evidence no picture of a disease would really be complete. This is interesting because what is happening in 1961 is applying a different set of rules to decide if there is an association as compared to 1943. In other words, the rules were changing at the same time knowledge was developing.

This type of commentary is not indexed and calls for reading lots of journals, many of them weeklies. My student has read all issues of the Lancet (which is probably the leading medical journal in the world), the British Medical Journal, and the Journal of the American Medical Association back to 1935 and has picked out a lot of material that I can't present here today. So far we've gotten up through 1961. After that it really gets tough because the

volume of literature exploded after that date, particularly after the 1964 conference in New York. I'm simply giving you some idea of the type of project that Guy has launched us upon, what this project involves, and where we are at present. Incidentally, we've located some very humerous stuff. For example, in 1949 Ovaltine was being advertised to prevent pneumonociosis and asbestosis. So we've come a long way since 1949.

Let me now proceed to something quite different -- and this is stimulated by an article I saw in this morning's paper. It's the matter of how much disease will be produced from exposure to asbestos. We've been working on a model to predict how much disease is produced with continuous exposure at any given fiber level over any given period of time. For example, we could think of workers who start at age 20 and who work for 50 years at 2 fibers per cc. How much disease would we expect to occur? This is really the important question, I think. What will happen to people if we take certain actions on their behalf at this point in time?

First, to review rapidly some elements of carcinogenesis needed to develop a model, we know that if you're exposed to a carcinogin, you won't get cancer tomorrow, but that there will be a peak incidence at some future date and thereafter it tapers off. This distribution seems to follow a mathematical function called a log normal.

Another important notion for modeling the effects of asbestos exposure is that for low dose rates the time it takes for cancer to appear will be very long. On the other hand, if you have a very high dose rate, cancer will appear rather quickly. I'm thinking now about groups of people, say 100,000 people exposed at different levels. In other words, there is a relationship between

the intensity of exposure and the latent period. Thus, a population would have to live a long time to experience a full response to exposures at very low levels.

Now if we add to this the assumption that this dose-response relationship is linear, we can develop the family of response curves. The linear dose-response idea means simply that every increment of dose causes a like increment in response -- a straight-line relationship. That has some acceptance as far as cancer is concerned. It's one that you may not like, however, because it means that any little bit of asbestos will produce some kind of response given enough people and enough time. If you talk about a threshhold limit, the idea is that a little bit won't produce anything -- that you have to have a certain amount - 2 fibers, 5 fibers, etc., before you produce any disease. I don't think it really works that way. I think that any little bit does produce something.

Here is the output of the model, and is kind of the end product.

Slide #3

Cumulative Relative Risks for Respiratory Cancer at Seven Levels of Continuous Exposure

Exposure Level (f/cc)	20 Year	40 Year	60 Year
1/2	1.000	1.000	1.003
1	1.000	1.003	1.021
2	1.000	1.026	1.098
4	1.005	1.154	1.361
8	1.050	1.684	2.075
16	1.390	3.400	3.702
32	3.291	7.861	7.032

Unfortunately, in the interest of time, I've had to skip some intermediate steps and assumptions but could provide these to anyone interested. This says that where the cumulative relative risk is carried to three decimal places, no effect of asbestos on the death rate from lung cancer can be detected until 60 years of exposure at 1/2 fiber, 40 years at 2 fibers, and 20 years at 4 fibers. One reason for this is the assumed long latent period for low doses. After 60 years, for example, increased lung cancer would appear; but, of course, for persons entering the labor force in their 20's, other causes of death are pretty important at this point.

Now that we know what the risk is at various exposure levels, we could calculate absolute number of cancers if we knew how many people were exposed. I went back to something the Asbestos Information Association did some time ago and made a slide of it. Here are quotes from Irving Selikoff about how many people are exposed and how many will die from asbestos-related diseases.

Slide #4

Dr. I. J. Selikoff . . . . Predictions

	No. of Workers	Description of Cohort	Total Deaths from Asbestosis Lung Cancer & Mesothelioma
Article in Wall Street Journal -- 6/8/72 "Studies by Dr. Irving Selikoff ... Lead Him To Predict..."	250,000	All workers currently Employed in the Asbestos Industry	85,000*
Article in the New York Times...6/13/72 (Five Days Later) "If our experiences.... Guide...."	500,000	All workers currently and previously employed in the Asbestos Industry	170,000
Testimony at Toxic Substances Hearing - Our studies indicate.."	1,000,000	All workers currently, previously, and who will be employed in the Asbestos Industry in this country	340,000

*Actual Quoted Prediction was 95,000, But this included deaths from GI Cancer

This is essentially the material that was quoted in this morning's paper and apparently assumes that all persons exposed have been and will be exposed like men in his studies -- mostly asbestos insulators. We hope that isn't so. What we'd really like to know is how many men would be affected by asbestos if exposures were at 4 fibers, 2 fibers, etc., since that is what the government is deciding.

Let's just take one number. Let's take the first number, 250,000 -- that's all workers currently employed in the asbestos industry. One question we might ask is how many of these people would you expect to die of lung cancer if there was no asbestos around. Let's say they never had been and never would be exposed to asbestos. Of course, some people would still die of lung cancer because lung cancer has lots of causes -- cigarettes, air pollution, etc. Also, you have to remember that things can happen to you other than dying of lung cancer. You could get hit by a truck or have a heart attack (some people are going to have a heart attack when they read some of this stuff).

I estimate that if there was no asbestos exposure, in a group of 250,000 men there would be 12,500 dying of lung cancer. Now, what if these men were exposed continuously to half a fiber for 60 years? From Slide #3, we can estimate that 12,537 would die of lung cancer (1.003 x 12,500). If these 250,000 men were all exposed continuously to two fibers, 12,762 would die; if exposed to four fibers, 17,012 would die, and if exposed to eight fibers, 25,937 would die of lung cancer. This is after 60 years. Looked at another way, 250,000 men exposed for 60 years to half a fiber will produce 37 lung cancer deaths, etc.

The problem then comes down to these excess deaths and how many there are at these different exposure levels. To simply deny that there are any excess deaths I don't think is ever going to get any place, but I think to recognize how many we're talking about may have some meaning. Given improvements in industrial hygiene, I'm sure we're not talking about excesses of the magnitude Dr. Selikoff predicts. Of the 500,000 he predicts will enter the industry or will be exposed during the remainder of the century, a 2 fiber standard at 40 years of continuous exposure would increase deaths from 25,000 to 25,650.

Let me show you my last slide which is a check on how well my model actually predicts.

Slide #5

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

Does my model predict Selikoff's finding? These data are from Selikoff's study of 17,000 insulation workers. Selikoff has undoubtedly produced some of the most magnificent epidemiological data I've seen, and I think this 17,000 insulation workers study is truly a great study. You see there is a very good correspondence. The model predicts pretty much what Selikoff observed. Notice, for example, that Selikoff observed less and less cancer as time went on. That's what the model predicted too. Notice that his peak occurred for men who were exposed 30-34 years ago, and I get exactly the same peak.

To summarize, it is possible based upon the epidemiological data now available to predict what will happen if various actions are taken at this time in regard to asbestos exposure and if various standards are set. This should be helpful in deciding where you want to set this thing. I think it would be sticking our heads in the sand to say that nobody will ever be affected at 2 fibers or at any other finite level.