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April 12, 1993

Robert Grahek
Director Safety and Industrial Health
The Geon Company
6100 Oak Tree Blvd.
Cleveland, OH 44131

Re: Vinyl Chloride Program

Dear Mr. Grahek,

In October, 1992, we began to review the Geon Division's occupational health experience related to employee exposure to vinyl chloride monomer. The purpose of this project was to provide Geon management with an overview of the following:

- the health impact of current and past exposure to vinyl chloride at Geon facilities.
- current facility medical programs, in relation to OSHA mandated medical surveillance of vinyl chloride exposed workers.
- the BFGoodrich Medical Surveillance System and the data base at the University of Louisville as they relate to the health of Geon employees.

Methods

Information was obtained through review of BFGoodrich files, literature searches, and interviews with plant and Division personnel. Plant visits were made to Louisville (11/17-19/92) and Avon Lake (12/7/92 & 1/12/93). Meetings and follow-up discussions were held with Dr. Carlo Tamburro, a specialist in liver research at the University of Louisville.

Health Effects Attributed to Vinyl Chloride Exposure

Three primary health effects have been attributed to exposure to vinyl chloride monomer. These are:

- Angiosarcoma, a rare form of liver cancer.
- Liver damage, or chemical hepatitis.
- Acro-osteolysis, an erosion of the bones in the fingers.

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Cases of angiosarcoma have been tracked and recorded in the Angiosarcoma Register, maintained in a cooperative fashion by United States and European PVC producers. As of February, 1991, 39 cases have been reported in the United States. Of those, 16 (41%) have occurred at Geon facilities. Fifteen of the cases occurred at Louisville, the other at Avon Lake.

While the first Louisville case occurred in 1964, the majority were diagnosed in the mid-1970's. Only four cases have occurred since 1980, the last being diagnosed in 1987. This is summarized below.

Table 1. Angiosarcoma of the Liver by Year of Diagnosis,
Geon Cases in the United States

<u>Year of Diagnosis</u>	<u>Cases</u>
pre 1965	1
1965 - 69	2
1970 - 74	6
1975 - 79	3*
1980 - 84	3
post 1985	1

* Avon Lake case

All but one of the cases resulted in death within two years of diagnosis. One employee diagnosed in 1982 is still living with no evidence of disease 10 years after surgical treatment. In the Register, only three others are alive out of a total of 157 cases reported.

The majority the Geon cases first worked with vinyl chloride prior to 1955. No case has occurred in Geon employees who first worked with vinyl chloride after 1962. There is only one case in the Angiosarcoma Register whose first exposure to vinyl chloride occurred after 1970. The first exposure for the Geon cases is summarized below.

Table 2. Angiosarcoma of the Liver by Year of First Exposure to
Vinyl Chloride, Geon Cases in the United States

<u>Year of First Exposure</u>	<u>Cases</u>
pre 1945	2
1945 - 49	5
1950 - 54	5*
1955 - 59	3
1960 - 65	1
post 1965	0

* Avon Lake case

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Non-malignant liver disease has been less well-documented in vinyl chloride exposed workers. During the initial screening in Louisville in 1974, 124 employees were identified with blood test or liver scan abnormalities and were referred for liver biopsies. Non-specific findings (focal hyperplasia of liver cells) were attributed to vinyl chloride in approximately one fourth of those biopsied. Many employees had normal liver biopsies or findings, such as fatty accumulation, which were not related to vinyl chloride exposure.

As a result of the screening program at Louisville in 1974, several employees were restricted from vinyl chloride exposure. Twelve Louisville employees remain on active workers' compensation logs for "liver damage."

In contrast, there were few employees referred for further evaluation from a similar screening program at Avon Lake. No Avon Lake employees have been diagnosed with non-malignant liver disease due to vinyl chloride exposure. Other than the one case of angiosarcoma, there have been no claims of liver damage in Avon Lake employees.

Both Avon Lake and Louisville performed hand x-rays in the mid-1970's to screen employees for acro-osteolysis. While the exact numbers are not available, several employees with this condition were diagnosed at both locations. Cases were followed with serial x-rays and the condition was found to be reversible. Long term sequelae have not been evaluated. None of the employees who developed angiosarcoma were known to have had acro-osteolysis.

Plant Program Activities

Louisville

Louisville has conducted examinations since the mid-70's. Initially the program consisted of annual liver-spleen scans. Abnormal scans resulted in 124 liver biopsies being performed at the University of Louisville. Dr. Carlo Tamburro has retained clinical and pathologic information on all of these employees, including those diagnosed with angiosarcoma.

Beginning in the late 1970's, a periodic examination program was arranged with the School of Medicine at the University of Louisville. The plant nurse conducted blood tests, urinalyses, hearing tests and lung function tests in the plant medical department. Blood tests were performed twice each year for employees with over 10 years of exposure to vinyl chloride. The results were reviewed by the plant physician, Dr. John Creech. Those with abnormal results had the tests repeated. Those with persistent abnormalities were referred to the University of Louisville.

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Annual physical examinations have been conducted by medical students from the University of Louisville. These have consisted of a standardized health questionnaire and a hands-on examination at the plant. According to the nurse, participation in the examinations has decreased over the years, although most employees continue to participate in the blood testing. Information from these examinations has been collected in a computer system at the University of Louisville under the direction of Dr. Tamburro.

The laboratory testing and physical examination components of the Louisville program have not been well-coordinated. The University of Louisville does not have any blood, urine or lung function test results in their data base. The BFGoodrich Medical Surveillance System does not have the information from the hands-on examinations.

Dr. John Creech remains the plant physician in Louisville. Dr. Creech was the surgeon who diagnosed several of the initial cases of angiosarcoma. Following the mass screening program in 1974, most of the cases were diagnosed after the development of symptoms, rather screening tests. Both Dr. Creech and Dr. Tamburro have questioned the value of the OSHA mandated examination and testing program. Dr. Tamburro has published his views.

Avon Lake

The program at Avon Lake had similar beginnings. Liver-spleen scans were also conducted, although the number with abnormalities was much lower. The plant physician, Dr. Nepomacino, has been at the facility since 1974. He was unaware of any liver biopsies being performed.

The plant began a regular program of testing and examinations in the late 1970's. The nurse has conducted blood tests, urinalyses, hearing and pulmonary function tests on a single visit. The employee returns to the medical department for a physical examination after the test results are available. Abnormal liver tests are repeated, but if they persist, the employee is referred to their personal physician. Participation in all aspects of the program at Avon Lake has remained high (approximately 90%).

Research Activities: University of Louisville

Dr. Tamburro has collected historical exposure information for 22 chemicals used in Louisville back in the late 1970's. Using a technique of rank-ordering the exposures, he has calculated the cumulative exposure rank months (CERM) for each chemical. He has then compared the rank order exposures of employees with angiosarcoma to control employees without liver disease.

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Using this technique Dr. Tamburro identified a significant association between angiosarcoma and higher rank order exposures to four chemicals: vinyl chloride monomer, hexane, catalysts (all used in all vc polymerizations), and diethyl maleate (catalyst used in specialized reactions). While confirming the association between vinyl chloride exposure and angiosarcoma, the other findings are of uncertain significance. These findings were reported in 1981.

In addition, Dr. Tamburro has also been investigating dose-response relationships for vinyl chloride-induced angiosarcoma. Using the Louisville data and information from the Angiosarcoma Register, Dr. Tamburro has noted an unusual relationship between year of exposure (and presumed "dose") and latency. Those first exposed in early years (prior to 1950) had higher exposures (estimated to be > 750 ppm) had a longer latency period while those exposed later (1950 - 61) had lower exposures (250 - 750 ppm) and a shorter latency. Latencies have gradually fallen from 1940 - 70 from an average of 35 years to 14.6 years. Dr. Tamburro has used this information, and histologic data from persons he has followed, to propose a biological threshold of approximately 50 ppm, below which there is no risk of liver disease or cancer.

Dr. Tamburro has also written several articles on the use of liver enzymes in screening workers at risk. His past reviews have failed to demonstrate significant value in the use of the standard liver enzyme panels required by the OSHA vinyl chloride standard. These tests lack both the sensitivity and the specificity needed to properly identify persons at risk. In addition, early detection has not been shown to increase survival for those who do develop angiosarcoma.

BFGoodrich Medical Surveillance System (MSS)

The BFGoodrich MSS contains the results of employee work histories input from the personnel system dating back to 1976. This also contains information from medical questionnaires and the results of blood, urine, lung, and hearing tests conducted at BFG plants.

The system has also stored diagnostic codes (International Classification of Disease, Ninth Revision, or ICD-9) from health insurance claims, death certificates and employee medical examinations. The system has the capability of calculating morbidity (illness) or mortality (death) rates in employee populations. These may be grouped by facility, department or job. The system can also analyze test results (normal/abnormal) to evaluate trends in employee groups.

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DISCUSSION

In the 1970's, a relationship between exposure to vinyl chloride monomer and angiosarcoma of the liver was recognized. The BFGoodrich Louisville plant was one of the first locations to identify cases. As a result, a systematic program of testing and examinations was established and the results were computerized in a central system.

Although a relationship between vinyl chloride exposure and angiosarcoma of the liver is widely accepted, several characteristics of this relationship remain obscure. While cases have occurred throughout the world, certain plants appear to have a much higher risk than others. In North America, only 13 of 29 PVC operations which started prior to 1962 have recorded cases of angiosarcoma. Only four operations have recorded more than one case and the majority of the cases have occurred at three locations (Louisville, 15; Shawinigan, 12; UCC Charleston, 9). This clustering of cases at has also been observed worldwide, where only 20 of 32 operations have reported cases and only 10 have reported more than one.

A review of the BFGoodrich experience raises several questions. The Avon Lake and Louisville plants opened within several years of each other and were similar in size and manufacturing operations. While the number of cases of acro-osteolysis was similar, the incidence of angiosarcoma and liver damage have been markedly distinct. This appears unlikely to be a chance occurrence, and suggests the strong possibility that certain co-factors, in addition to vinyl chloride, were necessary to induce disease.

The findings from Dr. Tamburro's research are intriguing in this regard. Animal studies have shown that glutathione, a sulfur rich scavenger of free radicals, is involved in the detoxification of vinyl chloride. Diethyl maleate, a chemical used in certain PVC operations, depletes the liver of glutathione, making the liver more susceptible to damage. The association of exposure to diethyl maleate with angiosarcoma, reported in Dr. Tamburro's rank exposure study at Louisville, may well be the key observation which explains the variable risks seen in Geon operations, and throughout the world. This mechanism would also explain the anecdotal observation that excessive alcohol intake also contributed to the disease risk (since alcohol would also deplete the liver of glutathione).

If a co-factor is critical to development of angiosarcoma, this would also explain the inverse latency findings. If the co-factor was introduced later in production (such as the mid-1950's), this would give the appearance of a shorter latency (based on time of first exposure to vinyl chloride) for those exposed later. The key would be to determine latency from first exposure to the co-factor, not just vinyl chloride.

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The further investigation of these observations is important for several reasons. This will allow better management of the ongoing vinyl chloride medical examination program by only screening the employees who are truly at high risk. Currently, the majority of Geon production employees are screened annually, with over half the employee population screened biannually. A better understanding of risk will allow the program to focus on a much smaller population. Activities which have no use in protecting employee health can then be eliminated.

Another potential benefit is that the proper characterization of the carcinogenic risk, including the identification of co-factors and a biological threshold, will allow more meaningful occupational and environmental risk assessment. Clearly, the Geon angiosarcoma experience argues against any simple model of carcinogenic risk related to vinyl chloride.

RECOMMENDATIONS

To further investigate these issues I recommend that the following actions be considered:

- 1.) Further work in collaboration with the University of Louisville

I recommend that the method of exposure ranking performed in Louisville be applied to other facilities. This can be used to determine the relationship of angiosarcoma and liver disease to exposure to diethyl maleate. Dr. Tamburro has indicated that this material was also used at the Shawinigan Plant, another facility with a very high risk of disease. If this finding is verified, the pathophysiology of vinyl chloride related disease will be much clearer. This will also have implications for chemical carcinogenesis and risk assessment, in general.

Geon should also consider providing Dr. Tamburro with the medical test data from the BFG MSS. They will be able to perform analysis of the liver enzymes to further define the utility of this type of testing in ongoing medical monitoring.

- 2.) Case Analysis

Geon has sufficient numbers of cases of angiosarcoma, liver damage, and acro-osteolysis to conduct a case control analysis of risk factors and outcome. In addition, the review of the case histories, will provide an assessment of the value of the current screening programs. This review will likely demonstrate that annual screening for weight loss or abdominal pain in employees who are truly at risk for angiosarcoma is much more cost-effective than annual, or biannual liver enzyme testing in the employees in general.

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3.) Compilation of All Data

The results of the initial screenings in 1974 need to be assembled. This includes all the liver-spleen scans and all the hand x-rays (for acro-osteolysis). Comparing the findings at the time from the two facilities (Avon Lake and Louisville) will be essential in evaluating subsequent outcomes. If both facilities had similar numbers of workers with acro-osteolysis, this would indicate that either acro-osteolysis was not due to vinyl chloride, or that angiosarcoma was not due to vinyl chloride exposure alone.

4.) Analysis of MSS Data

The MSS can be used to update the morbidity and mortality experience of employees based their vinyl chloride exposure intensity or exposure to co-factors. This will require the proper categorization of employees based on historical exposure profiles. At present, the MSS lacks this information. In addition, the system has never been used to analyze employee populations grouped by this type of categorical exposure risk (the system currently uses current jobs and locations in reporting). If this can be accomplished, the true value of the system in evaluating long-term health risks can be better evaluated.

In the course of this review, I have assembled the available occupational health literature on vinyl chloride. There has been very little published in many of the areas I have outlined. Most of the current research has consisted of updates on large mortality studies. I believe that further investigation into possible co-factors will generate a tremendous amount of interest in both industry and the scientific community.

I look forward to continuing to work with the Geon Company on this. If you have questions or comments, please contact me.

Sincerely,

D. R. Lewis, M.D., MPH

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