Firestone

INTEROFFICE

DATE AUGUST 30, 1976

TO DR. R. S. BROOKMAN FROM R. A. PARK

REFERENCE

SUBJECT SYNOPSIS OF PAPERS PRESENTED AT SEPTEMBER 12, 1975 CONFERENCE OF ROYAL SOCIETY COVERING VINYL CHLORIDE HEALTH HAZARDS

Reference: Letter to VCM/PVC Producers Group from John Lawrence (SPI), dated 6/2/76.

Executive Summary

Fourteen papers (36 pages) presented at the September 12, 1975 conference on vinyl chloride health hazards, are abstracted from the Proceedings of the Royal Society of Medicine (London).

"The purpose of the present symposium is to review British experience of the environmental, clinical, epidemiological and pathological effects of exposure to vinyl chloride arising in the course of polymerization of vinyl chloride monomer to polyvinyl chloride, and to exchange information. . ."

A copy of the paper presented by Dr. Henry Falk and Mr. Richard J. Waxweiler is attached in its entirety. This paper gives "preliminary review of the results" of joint Firestone, University of North Carolina, NIOSH-CDC medical screening examination of 530 workers at Pottstown.

Subject papers were published in the Proceedings of the Royal Society of Medicine, Vol. 69, p. 16 - 52.

Originals are on file in library. (Copies available upon request.) Highlights follow:

Title: "Vinyl Chloride" by Dr. Suzette Gauvain.

Primary purpose of this paper is to summarize events leading up to current vinyl chloride interest with emphasis upon events in Great Britain.

"The purpose of the present symposium is to review British experience of the environmental, clinical, epidemiological and pathological effects of exposure to vinyl chloride arising in the course of polymerization of vinyl chloride monomer to polyvinyl chloride, and to exchange information. . ."

"The medical aspects of the code are contained in parts 12, 13 and 14. Part 12 defines 'supervised workers'. Part 13 is concerned with their medical supervision. Supervised workers should undergo pre-employment medical examination. Those already employed should be examined, if this has not been previously done, within twelve months. The examinations should be repeated annually, and should include: (1) a full medical and occupational history; (2) a clinical examination with particular reference to the abdomen, skin and extremities; (3) X-ray examination of the hands; (4) such further tests as may be indicated by the above procedures or may be recommended in supplements to the Code. The leaflet describing the early effects of vinyl chloride monomer should be given to the supervised workers at this examination unless issued previously.

"The physician engaged to provide medical supervision for the workers should see a supervised worker who reports symptoms which may be due to exposure; he or she should see a supervised worker who has been absent from work more than two weeks owing to illness. These absences should be reviewed on a group and individual basis. If indicated, medical examination should be undertaken at any time. Section 16 provides for the keeping of confidential medical records of all supervised workers; these must not be destroyed without the agreement of the Chief Employment Medical Adviser. . ."

"The Working Group on Vinyl Chloride Code of Practice for Health Precautions met on 8 October 1975 and adopted a new hygiene standard agreed by the Working Group as 'a ceiling value of 50 ppm and a time weighted average of 10 ppm, allowing that wherever practicable exposure should be brought as near as possible to zero concentrations.' The figures of 50 parts/10^6 and 10 parts/10^6 replace the original figures of 50 parts/10^6 and 25 parts/10^6. . ."

Title: "Vinyl Chloride and the Production of PVC" by Mr. A. W. Barnes.

This paper discusses the polymerization technique for PVC and "interfaces between vinyl chloride and people."

". . . That the polymerization section is in fact the area where hazard has existed in the past is confirmed by the fact that all the authenticated cases of vinyl chloride-related angiosarcoma of the liver throughout the world have been of workers engaged in plants where liquid vinyl chloride under pressure was used in large quantities. . ."

"The general consensus of opinion throughout the world, today, is that average atmospheric exposure for polymerization workers between 1940 and 1970 might have been of the following orders: 1945-55, ~1000 parts/10^6; 1955-60, ~400-500; 1960-70, ~300-400; mid-1975, ~50; 1975, ~5 parts/10^6. Across the world,

there will have been variations around these figures because of differences in plant design or process operation. Even the way in which jobs were organized can have caused variations. In some countries or on some plants workmen were employed specifically to clean out autoclaves (where exposures could have been very high) while in others autoclave cleaning was part only of a whole range of jobs carried out by individual work people. Some spokesmen have suggested, perhaps for full-time cleaners, exposure levels as high as 5000 parts/10^6 in the early days of the industry. . ."

"Table 1
Vinyl chloride monomer levels in UK industry

Polymerization	January 1974 (parts/10^6)	July 1975 (parts/10^6)
VCM in plant atmosphere (weekly average)	~150	~5
VCM emissions	0.75% of output	0.3% of output
VCM in products	200-500	< 50 for most grades
Fabrication and Use		
VCM in plant atmospheres	2-15	<2
VCM in PVC bottles	~50	~2
VCM in beverages	0.1	0.001

"

"Table 2
Daily dosages at current and earlier exposure levels

	Daily dose (g/kg body weight)
Polymerization plant operator at 1000 parts/10^6	0.36
Polymerization plant operator at 500 parts/10^6	0.18
Polymerization plant operator now at ~5 parts/10^6	0.0018
Fabrication plant operator at 1 part/10^6	0.0004
Average UK citizen through ingestion in food	0.000000004

"

"In later papers to this conference, a wide range of diseases or symptoms which have been associated with or attributed to exposure to vinyl chloride will be discussed. It is important to note that most, if not all, of these have been contracted by people who worked under conditions represented by the highest figures in the above table. Today no one is exposed to doses at this level. The exposure of workers in industry is now at least two orders of magnitude lower, while the general public in the UK absorbs, through foodstuffs, a quantity which is some fifty million times lower. . ."

During the discussion of Mr. Barnes' paper, the following comments are recorded:

"It was in the drying and bagging sections of the PVC-producing process that exposure to solid PVC particles could arise but, despite extensive medical investigation, no significant abnormalities had been found among drier operators or packers. It was perhaps worth noting, too, that the greater proportion of PVC powder was of a particle size similar to sand so it did not generally pose an airborne dust problem. For those powders which might cause true dust exposures it had been customary in industry, because of the nuisance and discomfort factors alone, to provide some form of respiratory protection.

"Dr. C. S. Darke (Royal Infirmary, Sheffeld) said that he had investigated 14 cases of breathlessness in workers exposed to vinyl chloride monomer. . ."

". . .It might be of importance that some of the worst affected men were concerned in a polymerization process that yielded 'plastisol', a very fine PVC powder with particle size around 0.5 µm. These particles, containing vinyl chloride monomer, could be carried to the alveolar walls where they might be retained and thus set up a reaction of the type seen on light microscopy.

"Professor I. J. Selikoff (Mount Sinai School of Medicine City University of New York) said that pulmonary abnormalities had been unexpectedly common findings among some 1200 vinyl chloride polymerization workers in his studies. Obstructive pulmonary function defects were noted in approximately 50%. Neither age nor cigarette smoking served to explain the findings. For those under age 40, obstructive findings were predominately among cigarette smokers, as expected. After that age, however, the prevalence of changes was very much the same among smokers and nonsmokers. Of course, age correlated strongly with duration of employment. These two factors were analysed separately and it was found that the changes were generally among smokers with less than 20 years from onset of exposure, but that thereafter they were present in both smokers and nonsmokers. Radiographic changes were less common. Overall, 13.3% of 985 chest films showed linear, reticular or nodular changes characterized as 1/0 or 1/1 in the ILO U/C Classification. Dyspnoea was uncommon and signs or symptoms of chronic bronchitis were not striking (Miller et al. 1975, Miller 1975). . ."

Title: "Review of Animal Studies" by Dr. K. S. Williamson.

Highlights of this paper include:

"Purchase and his co-workers dosed Wistar rats daily by gavage at 300, 50 and 5 mg/kg for 6 months. Fourteen months from the

start of the experiment, a large proportion of the animals in the 300 mg/kg group and several of those in the 30 mg/kg group have been found to have liver tumours. Preliminary histopathological work suggests that some of these tumours are hepatocellular carcinomata, though further work is necessary before this can be confirmed."

"It is of some interest to compare the doses received by animals in long-term studies with calculated theoretical doses for men exposed to various shift-average concentrations of vinyl chloride at work (Table 3). Again the calculated figures are no more than very rough indications of dose, but they do give a useful measure for assessing the animal data.

Table 3
Men at work
Ventilation = 10 m^3 air per 8-hour shift
Weight assumed to be 70 kg

Parts/10^6	mg/m^3	Daily dose (mg/m^3 x 10)	Daily dose (mg/kg)	Annual dose (g/kg) (daily dose x 250)
500	1250	12500	180	44.6
100	250	2500	40	8.9
50	125	1250	18	4.5
10	25	250	4	0.9
1	2.5	25	0.4	0.1

"Green & Hathway (1975) and Watanabe et al. (1975) have studied the pharmacodynamics and metabolism of vinyl chloride using ^{14}C-labelled material given by different dosing methods to rats. Both groups have shown that the proportion of the dose retained and metabolized is greater following small doses than large, though the absolute amount metabolized falls with diminishing dose. . ."

"Three principal eliminative routes have been identified by both groups: expiration of unchanged vinyl chloride by the lungs, expiration as CO_2 by the lungs, and excretion of metabolites in the urine. The proportion of vinyl chloride eliminated by these different routes varies with dose. . ."

"Though many important animal studies are still incomplete, there is already a substantial body of evidence to show that vinyl chloride is oncogenic, and there are some intriguing indications of the possible mechanisms of this action. . ."

"Discussion
Dr. L Magos (MRC Toxicology Unit, Carshalton) said that the dose plotted against the log of the number of malignancies gave a

straight line, making it very difficult to draw any conclusion about the threshold or no-effect level, as the zero-effect level could theoretically never be reached.

"Secondly, Dr. Williamson's data on the metabolism of vinyl chloride depending on dose indicated that at low exposure levels a high proportion of vinyl chloride was metabolized and less was exhaled unchanged. This might mean that increasing exposure above a certain level would exhaust the biochemical ability of the organism to convert vinyl chloride to a toxic metabolite responsible for the carcinogenic effect.

"These considerations indicated that experimental data must be interpreted with the upmost care. . ."

"Inferences and conclusions: (1) From the fact that haemangiomas occurred in the liver, and not in the lung (the primary site of entry), it could be inferred either that little or no vinyl chloride metabolism to free radical occurred in the lung, or that there was ample free SH to scavenge the vinyl radical. (2) Most important, the liver had a built-in antagonist to the vinyl free radical that provided the basis for a threshold for the carcinogenic response, in this case a threshold for an occupational carcinogen demonstrated by a specific biochemical constituent reaction. This finding explained the fact that among the tens of thousands of workers exposed only a small handfull of haemangiomas had been found. (3) Finding an oncogenic threshold of appreciable magnitude (between 50 and 10 parts/10^6) removed concern about general exposure of the public to small amounts (see Barnes, p 280) of vinyl chloride in PVC plastic wrappings of foods; the United States FDA could forget it!(4) To bolster resistance to effects of vinyl chloride, vegetables of the Brassica family should be eaten. Factors reducing free SH were: certain industrial exposures that were detoxified by cysteine, e.g. brombenzene; substances or conditions, e.g. certain chronic diseases."

Title: "Clinical Aspects of Vinyl Chloride Disease" by by Dr. B. J. Preston, et al.

Arco-osteolysis is defined as "dissolution of extremity of a bone and it is applied to the distal phalanges of the hands, feet. . ." Paper presents the radiological findings in four patients who had been involved in the production of PVC.

"All patients had the following regions examined by plain film radiography: hands, feet, shoulders, elbows, knees, ankles, pelvis, chest, skull, mandible and spine. Case 1 (AD) also underwent a barium swallow, meal and follow-through, angiography of the hands and serial films of the hands at 6 months and 2 years after presentation, and a film of the pelvis at 2 years. . ."

"These 4 cases show the wide radiological spectrum that may be encountered in men complaining of symptoms which could be related to their work in the polymerization of vinyl chloride. In Cases 3 and 4, no specific changes were encountered; in Case 2 only moderate changes were recorded whilst in Case 1, extensive bony changes were documented. Indeed, in Case 1, most regions of the body were involved and a review of the literature revealed that no previously reported case had such extensive bony changes. It has been suggested that personal idiosyncrasy may be an important factor in the wide variation of the radiological findings (Wilson et al. 1967). . ."

"Ross (1970) stated that the bone changes regress after the sufferer is removed from the hazard but in our Case 1 the serial films of the hands, feet and pelvis indicated that the acro-osteolysis was extending. Fragmentation of the remaining tufts has been described as part of the healing stage by Wilson et al. (1967), but in our Case 1 it was only in the distal phalanx of the left big toe that there was any definite evidence on the 2-year film to indicate bony regeneration."

Title: "Clinical Aspects of Vinyl Chloride Disease: Skin" by Dr. Anne E. Walker.

"The study covers 37 men aged between 26 and 59 years (average 50 years 2 months). Length of employment at the plant ranged from 9 months to 5½ years (average 2 years 8 months). Thirty workers had at some time been reactor operators, 4 were maintenance men, 2 worked as 'baggers' and 1 was a warehouseman. . .

"The commonest complaint was of excessive fatigue: men claimed to be excessively fatigued after minimal exertion and also reported somnolence. Coldness of the hands was also a frequent complaint."

"Obviously these subjective symptoms were difficult to evaluate or measure. However, one feature was noteworthy: 36 of the 37 stated that on at least one occasion they had felt overcome by the vinyl chloride fumes, describing themselves variously as 'unsteady', 'slightly drunk'and 'rubbery-legged', and this suggested that the men had been intermittently exposed to very high levels of VCM, which in experimental studies produces anaesthesia. These symptoms were most frequently experienced when men were hosing down the reactors during emptying, but also by men when inside cleaning the empty reactor, and by maintenance men when unblocking pipes carrying VCM.

"None of the 37 men had evidence of sclerodermatous skin change. One man previously employed at the plant had extensive sclerodermatous skin change affecting the hands, forearms, face, truck, thighs and dorsum of the feet; additionally he had extensive

lytic lesions of the bones, phalanges, feet, pelvis and jaw (K Lloyd-Jones, personal communication). In 5 men there was clinical evidence of Raynaud's phenomenon; in 2 it was a marked feature, with rapidly occurring colour changes from blue black to blanched white to a flushed pink. Individual fingers on the same hand might show a different colour change at any one time; on one occasion I observed a harlequin effect: the index finger was blanched white on the radial side and blue black on the ulnar side. Eight other men described symptoms of Raynaud's phenomenon but at examination only had rather cold hands. Coldness of the feet was a common complaint, but difficult to evaluate clinically.

"During the last year 4 men have shown some thickening of the skin with limitation of extension of the fingers and mild 'clawing' of the hands. These changes become more marked when the hands are cold.

"Of the 37, 4 developed a curious swelling of the face, largely periorbital and tending to improve in warmer conditions; the swelling was firm, and suggestive of scleroedema rather than scleroderma.

"Skin biopsies were obtained from the dorsum of the hand in 15 men. The epidermis and adnexal structures showed no abnormality. In the dermis there was some destruction of elastic tissue, but it was probably a normal age change. In one man with severe Raynaud's phenomenon the dermal arteries showed some medical thickening."

"Dr Marcus M. Key (University of Texas School of Public Health, Houston, Texas) asked if baggers and warehousemen had previously worked as reactor cleaners."

"Dr Anne Walker replied that they had not. Usually men started as baggers and later became reactor operatives and cleaners. The one warehouseman had never been in a reactor. One of the baggers had spent an initial training period as a reactor cleaner but had felt nauseated whilst in the reactor. After the first two weeks he had worked entirely in the dry building for four years. The other bagger was an epileptic and had never been in a reactor."

Title: "Evidence of an Immune Complex Disorder in Vinyl Chloride Workers" by Dr. A. Milford Ward.

With respect to the occurrence of Raynaud's phenomenon and loss of bone density in association with dermal thickening. . . "Recent studies have indicated that the disease process is not confined to the skin and skeletal tissues, but is a multi-system one with involvement of many organs and tissues."

"The major features of the disorder include hyperimmunoglobulinaemia, cryoglobulinaemia and cryofibrinogenaemia, and in vivo complement activation via the classic pathway with C4 and C3 conversion. There is, in addition, evidence for a reduced T cell population, with low spontaneous sheep cell rosette counts, and an increased B-cell population, as evidenced by an absolute increase in lymphocytes showing membrane bound immunoglobulins. The total lymphocyte counts are usually normal or slightly increased. Some patients show non-organ-specific antitissue anti-bodies of low titre but rheumatoid factor is universally negative.. ."

"The association of these experimental data with the observed immunological profile allows the construction of a theoretical model of the disease process. The initiating sequence is at present speculative and remains to be proven by further study, but the later sequence of events can be adequately explained by the immunological abnormalities. . ."

"The frequency with which abnormalities have been detected in this series, especially in that group in whom there were no overt clinical signs, suggests that the disease process may be more common than generally supposed. The theoretical, and at present speculative, initiating sequence of reactions in this disease process also raises the question whether other unsaturated halogenated hydrocarbons may also be involved in a similar chain of events."

Title: "Chromosomal Effects in Peripheral Lymphocytes" by Dr. I. F. H. Purchase, et al.

". . . In common with other carcinogenic chemicals, such as benzene, recent studies have demonstrated that workmen exposed to vinyl chloride have an increase in the percentage of lymphocytes with chromosomal abnormalities." "Studies of this type carried out on lymphocytes recovered from peripheral blood provide an easy clinically applicable method of assessing damage to living cells caused by carcinogenic chemicals. If there is a quantitative relationship between the percentage of chromosome abnormalities and the amount of exposure to the chemical, the estimation of chromosome abnormalities may provide a useful tool for determining levels of exposure which do not produce this mutagenic effect.

"We have studied a population of 80 workers including exposed workers, nonexposed workers from the same industrial site, and nonexposed control subjects from another environment. . ."

"The induction of chromosomal abnormalities is indicative of a mutagenic effect of vinyl chloride. It is important to know whether vinyl chloride is capable of inducing mutagenic effects in other test systems and particularly whether such an effect is produced on germ cells. Accordingly vinyl chloride was examined for dominant lethal effects in mice. Groups of 15 male

mice were exposed to 3000,10000 or 30000 parts/10^6 of vinyl chloride for 6 hours per day for 5 consecutive days. Each male was mated with 2 virgin females per week for 8 weeks and the females were killed at 13 days and examined for dominant lethal effects. There was no significant increase in any of the parameters (early deaths per implantation, early deaths per pregnancy). Vinyl chloride, therefore, did not produce dominant lethal effects in mice, indicating that it did not produce a mutagenic effect in germ cells even at these high levels."

Title: "Preliminary Results of Grey-Scale Ultrasonography in the Detection of Vinyl Chloride Related Liver and Spleen Disease" by Dr. K.J.W. Taylor, et al.

". . . a pilot project was carried out to ascertain whether ultrasound offered a possible noninvasive method for visualizing the liver and spleen in workers exposed to hepatotoxic agents. Initial results proved encouraging. . ."

"The liver is scanned in a series of paramedian sections illustrated in the schema shown in Fig 1. The resulting ultrasound scan is shown in Fig. 2. Ultrasound is a fast means of acquiring data. Using this single pass technique through the liver as shown in the diagram, good resolution is obtained without degradation by respiratory or cardiac excursions. This ultrasound technique involves no ionizing radiation nor other known hazards, no discomfort, and no need for contrast media. It does require considerable operator expertise and high quality instrumentation, which has only recently become commercially available. Machines which do not display the consistency of the liver are unsuited for examination of it.

"Nineteen volunteers were selected from the factory workforce, with varying exposures to vinyl chloride monomer. . ."

"These preliminary results suggest that ultrasound will result in a small incidence of false negatives (2 out of 19), so that the method is complementary rather than a replacement for current techniques. Both acquiring the ultrasound scans and interpreting them requires operator expertise, but automated scanners should become available within the next year, while experience can be gained if the potential of the method is sufficiently promising. Preparations are currently being made for a more extensive investigation of the application of grey-scale ultrasonography to detect any liver pathology in a community in the United States which has been heavily exposed to air pollution with VCM, as well as in workmen exposed during the course of their employment. . ."

Title: "Collagen Studies in Acro-Osteolysis" by Dr. M. I. V. Jayson, et al.

"The skin changes of acro-osteolysis (AOL) are in many respects analogous of those of scleroderma. In both conditions there is severe rigidity and thickening of large areas of skin, suggesting qualitative or quantitative changes in the collagen. . ."

"By both crosslink analysis and by measurement of ^{3}H-proline incorporation into hydroxyproline, we have confirmed excess new collagen synthesis in the skin of a patient with AOL. These results are analogous to the findings in the skin in scleroderma and account for the thickening of the skin. It is possible that the effect is generalized, and excess collagen proliferation in the blood vessels could lead to chronic ischaemia with ulceration of the fingertips and further local collagen production. Ischaemic necrosis could similarly occur in AOL and so produce the typical bone lesions."

"However, the AOL bone lesions differ in appearance from those of systemic sclerosis."

Title: "Epidemiological Studies of PVC Manufacturers and Fabricators, and Primary Angiosarcoma of the Liver" by Dr. P. J. Baxter

". . .The main aim of this survey is to evaluate the effects of this exposure in terms of mortality and cancer registration rates according to certified causes by including all past workers at every factory manufacturing PVC in Great Britain. Present and future workers are also to be incorporated. Identification details of the workers, including duration of employment and details of past exposure, are entered by the factory personnel departments onto individual survey cards according to instructions provided by EMAS. Past exposure had been graded into high (>200 parts/10^6), medium (>25 parts/10^6), and low (<25 parts/10^6), with 'constant' and 'intermittent' categories. The cards are updated annually and sent to EMAS headquarters. . ."

"The main aim of this study is to identify and verify all diagnosed cases of primary angiosarcoma of the liver occurring from 1974 onwards, and to evaluate their association with occupational exposure to vinyl chloride. . ."

"The controls, matches for age, sex and death register (locality), will be chosen from the other liver cancer deaths and also from deaths from all causes. Four liver cancer controls for each angiosarcoma case will be randomly selected by EMAS. The controls of deaths from all causes will be selected by the Registrar General's Office from the same death register as an angiosarcoma case. . ."

"In conclusion, prospective and retrospective studies are being carried out to provide a comprehensive assessment of the risk of occupational exposure to vinyl chloride and the development

of primary angiosarcoma of the liver. The prospective mortality and cancer registration studies will also permit the testing of hypotheses concerning the carcinogenicity of vinyl chloride in other sites, such as the lung and brain. And in the absence of a satisfactory objective test for use in morbidity surveys, mortality data should enable the more serious complications of periportal fibrosis due to vinyl chloride to be assessed."

Title: "Histopathology of Liver Lesions Associated with Exposure to Vinyl Chloride Monomer" by Prof. K. Weinbren.

"The tumour consists of cells which vary considerably in appearance but seem to have enough common features, particularly in their mode of growth, relationship to vascular spaces and stromal changes, to support the view that they are derived essentially from one cell type.

"In general the tumours show a gross appearance of dark haemorrhagic nodules in the liver; there is a variable distortion and apparent fibrosis in the intervening liver tissue. Sometimes foci are macroscopically less haemorrhagic. There is often frank necrosis."

". . .In sum, the tumour cell is distinguishable from hepatocytes, resembles cells normally associated with vessel walls and appears to be closely related to vascular spaces with variable degrees of abnormality.

"There are changes in other elements, both in tumour-bearing regions and in parts of the liver which appear to be free of tumour. These changes seem to involve mostly the supporting stroma. . ."

Title: "Epidemiological Studies of Vinyl Chloride Health Effects in the United States" by Dr. Henry Falk and Mr. Richard J Waxweiler.

Paper discusses history of vinyl chloride problem in USA; H/S surveillance; medical screening of vinyl chloride workers; cohort mortality study at four PVC polymerization plants.

Since the discussion of this paper includes reference to Pottstown, I am attaching the complete paper as "attachment A."

Title: "Medical Surveillance of Vinyl Chloride Workers" by Dr. B. W. Duck.

Paper describes medical surveillance program of Great Britain.

". . .A programme of action was discussed and agreed with medical representatives of Government and Trade Union agencies

and it was accepted that one of the main objectives was to gather clinical and epidemiological data to provide a reasonable foundation for future decisions concerning regular medical surveillance.

"The survey population was divided as follows: Vinyl chloride workers Group 1 - all autoclave floor workers, vinyl chloride monomer (VCM) production workers with five or more years' service; Group 2 - vinyl chloride monomer production workers with less than five years' service, all other VCM/PVC production workers. Controls - workers from same sites with no history of VC exposure.

"A standard medical examination procedure was adopted: Initial examination comprising medical history (questionnaire), physical examination, biochemical tests (SGOT, SGPT, GGTP, alkaline phosphatase, bilirubin), platelet count, urinalysis. Follow up of abnormal findings, with repeat biochemical tests and platelet count, and persisting abnormalities referred to consultant for specialist investigation.

"The programme was introduced simultaneously on the six production sites and the employees concerned were informed that it was not an individual screening test, but a joint investigation to provide data that would help to establish future medical policy. It was also explained that any individuals with suspicious findings, notably persistently abnormal test results, would be referred for appropriate specialist investigation by arrangement with their family doctors. . ."

". . .Hence interim findings only can be presented at this stage and no firm conclusions can be drawn until all the facts have been elicited and the mass of data obtained has been appropriately analysed. . ."

"Abnormal liver function test findings were relatively common in both vinyl chloride workers (12.5%) and controls (16.5%) even though results had to fall well outside (2 or 3 standard deviations) the normal range in order to be classified as abnormal. Repeat testing revealed persistent abnormalities in one third of the vinyl chloride workers in whom the initial findings were abnormal and these 56 men were referred for further investigation. Comparable data for the controls are at present unavailable."

Title: "Environmental Monitoring" by Mr. H. F. Henning.

Paper describes instrumental monitoring techniques; presentation of results; influence of peaks; influence of sampling frequency; other problems (preservation of records).

R. A. Park

RAP:blc

cc: Mr. T. C. Walker
Dr. F. T. Diao
Dr. L. H. Ballou - Akron

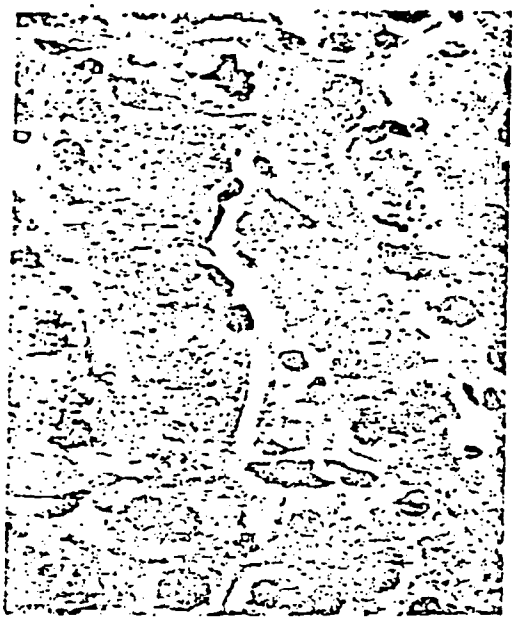

Fig 9 *Bizarre and enlarged sinusoidal lining cells and hepatocyte mitotic abnormality in same patient as Fig 8. H & E. ×600*

to be striking hepatocyte involvement, even with mitotic abnormalities (Figs 8–9).

The question whether these lesions are significant as premalignant changes is unanswered, as many of the alterations can be found in other conditions such as congestive cardiac failure, endothelial cell hyperplasia in cases of lymphoma, and of hepatocyte and other changes in many drug toxicity situations. Other pathogenetic questions also have to be posed, such as what is the primary lesion, which cell is involved in the formation of the tumour, what is responsible for the curious fibrosis and survival of the hepatocytes. Understanding these processes would probably enable us to make a better assessment of individual risk factors and perhaps to work out whether there is a tolerable exposure.

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Epidemiological Studies of Vinyl Chloride Health Effects in the United States

The vinyl chloride (VC) problem has had a considerable impact in the United States during the past year and a half. Perhaps related to the age and conditions of the VC industry, or simply to the sheer size of it, the United States has so far had the largest share of cases of VC-induced hepatic angiosarcoma (HAS); at the present time there have been 17 known cases in polymerization workers (Lloyd 1975). The finding of the initial cases was a dramatic event, and unlike what has occurred with many other proven or suspect carcinogens, the confirmatory experimental evidence arrived almost simultaneously with the epidemiologic results (Maltoni & Lefemine 1974). The widespread industrial applications and uses by the consumer were instantly appreciated, and since the VC problem also arrived at a time of growing awareness and concern among workers and consumers about environmental and occupational hazards, it served to focus these concerns.

Within the first few months after the initial cases were described a number of worrisome reports appeared. Investigators in Louisville, Kentucky, and also at Mount Sinai Hospital in New York demonstrated a high percentage of liver function abnormalities in polymerization workers, suggesting a broad problem (Makk *et al.* 1974, Lilis *et al.* 1975), and, in addition to this, the earliest mortality studies (Monson *et al.* 1974, Tabershaw & Gaffey 1974) suggested increased rates for nonhepatic tumours, parallelling the multiplicity of tumour types seen in experimental studies (Maltoni & Lefemine 1974). Review of records at the Connecticut Tumor Registry, started in 1935, revealed 5 definite cases of HAS; 4 cases were clustered in one industrialized area and had occurred since 1967; 3 of these (and possibly a fourth case where the diagnosis was uncertain after review of slides) occurred in workers at two polyvinyl chloride (PVC) fabricating plants or in residents living nearby (Landrigan & Heath 1976). Further concern was generated by

reports of the potential carcinogenicity of chemicals structurally related to VC, e.g. chloroprene (Lloyd *et al.* 1975) and trichloroethylene (National Cancer Institute 1975, unpublished data), and by the knowledge that VC workers in many instances have been exposed to multiple related chemicals, including vinylidene chloride and acrylonitrile (vinyl cyanide).

As part of the United States Public Health Service response to the VC problem, the National Institute of Occupational Safety and Health (NIOSH) and the Bureau of Epidemiology, Center for Disease Control (CDC), have worked on a number of VC-related epidemiologic projects during the past year and a half; in this paper we will briefly review some of the early results of three of these studies.

HAS Surveillance

A death certificate search for all cases of HAS recorded under ICD Code 197.8 (8th Revision), which encompasses various miscellaneous forms of liver tumour including most cases of HAS, was undertaken by CDC for the years 1966–73 in the United States. This search is almost completed, with only data for New York City not yet available at the time of this review.

Table 1 shows the number of cases of HAS and non-angio hepatic sarcomas by year of death for 1966–73; there is no evidence for an increase in the incidence of these malignancies during this period.

A review of the relative occurrence of hepatic sarcomas recorded under ICD Code 197.8 showed angiosarcoma to be the largest group (35% of total hepatic sarcomas), followed by sarcoma of unspecified type (31%), leiomyosarcoma (12%), fibrosarcoma (7%), and a grouping of miscellaneous sarcomas (15%).

Table 1

Hepatic sarcoma in the United States● by reported histology and year of death, 1966–1973

Year of death	*All sarcoma*	*Angiosarcoma*	*Non-angio sarcoma*
1966	31	9	22
1967	40	13	27
1968	23	9	14
1969	14	7	7
1970	31	15	16
1971	23	5	18
1972■	9	1	8
1973	25	9	16
	196	68	128

● From death certificates, ICD Code 197.8 (8th Revision). Data from New York City not included
■ Half year sample

Table 2

Hepatic angiosarcoma in the United States● by age at death and sex, 1966–1973

Age at death (years)	*Male*	*Female*	*Total*
0–9	2	2	4
10–19	1	1	2
20–29	1	1	2
30–39	5	4	9
40–49	7	2	9
50–59	13	2	15
60–69	5	5	10
70–79	11	3	14
80+	1	2	3
	46	22	68

● From death certificates, ICD Code 197.8 (8th Revision). Data for New York City not included

There was approximately 1 case of HAS for every 300 death certificates reviewed.

Table 2 demonstrates a male to female ratio of 2:1 for HAS. Sixty-two percent of cases occurred in the group aged 50 or more, with 26% in the 30–49 year age group. Non-angio hepatic sarcomas differed in having a male to female ratio of only 1:1, and an altered age grouping with 78% of cases aged 50 or more and only 9% in the 30–49 year age group. These differences are consistent with a hypothesis that occupational exposure may be a more significant factor in the causation of HAS than of non-angio hepatic sarcoma.

Only 2 of the patients with HAS in the death certificate review were recorded as having worked in PVC or plastics plants (1 PVC polymerization worker and 1 accountant in a PVC fabrication plant); both were cases which had been identified prior to this study. No other occupation is recorded more than twice except for the occurrence of 5 printers. Although all were subsequently confirmed as printers, a preliminary review of pathology records and specimens suggests that 4 of the 5 cases may have been incorrectly diagnosed as HAS.

CDC has supplemented the death certificate survey with an intensive case-finding effort, including a national mailing to all pathologists, state epidemiologists, and major cancer referral centres and tumour registries, seeking information on as many cases of HAS as possible diagnosed in the US during the years 1964–74. At the present time approximately 240 cases have been identified. Pathology specimens for about two-thirds of these are currently under review at the National Cancer Institute and the Armed Forces Institute of Pathology. An epidemiologic evaluation of all cases to obtain more detailed histories regarding

past occupations, toxic exposures, and places of residence is underway.

Medical Screening of VC Workers

Together with the Occupational Health Studies Group of the University of North Carolina, NIOSH-CDC recently concluded a cross-sectional medical screening examination of 530 workers at a plant in Pennsylvania which contains both a large tyre-building facility as well as one of the oldest PVC polymerization plants in the United States. Included in the study were approximately 130 current PVC polymerization workers and a similar number of control workers from the tyre plant who had never worked in the polymerization facility. The 2 groups were comparable in age, alcoholic intake, and socioeconomic background; the controls were chosen from those areas of the tyre plant where exposure to solvents and dusts was least.

Preliminary review of the results shows no significant differences between the 2 groups for any of the 6 liver function tests performed (SGOT, bilirubin, alkaline phosphatase, LDH, GGTP, and ornithine carbamyl transferase). Additional analyses based on levels of VC exposure, duration and type of job, and other subgroupings are being done; these preliminary results however do not suggest the occurrence of liver function abnormalities on a broad scale secondary to VC exposure. One should of course be cautious about generalizing from the results at a single plant, and it will be important to compare these findings to studies at other PVC plants. It is also important to realize that since liver function tests are relatively insensitive to the early finding of VC-induced hepatic disease (i.e. fibrosis), the results of this type of testing are not a reliable estimate for the prevalence of VC-induced disease. Liver scans were also performed on all workers with more than 10 years duration of work in the PVC polymerization plant, and no cases of HAS were detected. Some increase in frequency of palpable livers on physical examination was found, however, among VC workers. A full report of findings from this comprehensive medical screening study is in preparation and will be available shortly.

Cohort Mortality Study at Four PVC Polymerization Plants

One of the results of this NIOSH-CDC study was the demonstration of an increased SMR for respiratory system cancer among members of the cohort (Waxweiler *et al.* 1976). On preliminary pathologic review, it was also noted that of the 12 lung cancer cases all 8 for which pathologic specimens were available were either large cell undifferentiated or adenocarcinoma of the lung; if confirmed, this unusual cell type distribution may support the association between VC exposure and occurrence of lung cancer.

Table 3

Lung cancer among workers at PVC polymerization plants in the United States by histologic type and extent of VC exposure

	Extent of VC exposure			
Histologic type	None	Less than one year	More than one year	Total
Epidermoid	1	1	0	2
Small cell undifferentiated	0	3	0	3
Adenocarcinoma	1	1	4	6
Large cell undifferentiated	4	0	6	10
Unclassified	1	0	0	1
	7	5	10	22

There are, however, two additional features which should be considered in evaluating this potential relationship. When all of the workers at these 4 plants are considered, including those who were not part of the defined VC-exposed cohort, a total of 22 cases of lung cancer (out of 48) were available for pathologic review. The increased incidence of large cell undifferentiated and adenocarcinoma of the lung was seen in VC workers with more than 1 year of exposure, while a distribution more closely resembling the expected small cell predominance was seen for VC workers with less than 1 year of exposure. Interestingly, however, cases of lung cancer in non-VC workers at these plants, although small in number, appeared to have a cell type distribution which was also predominantly large cell undifferentiated (Table 3). In addition, unlike the situation for HAS in these plants where all but one of the cases were long-term reactor cleaners and operators, the workers with large cell undifferentiated and adenocarcinoma of the lung were distributed in a number of different job categories. As a result, cases of lung cancer seem not to correlate as tightly with VC exposure as cases of HAS and it is conceivable therefore that some additional chemical exposure at these plants may be working together with VC (or even separately) to produce this effect. Further studies are currently underway in an effort to confirm these preliminary pathologic findings.

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DISCUSSION

Dr Mitchell R Zavon (*Baton Rouge, Louisiana*) asked whether the clinical examiners at Pottstown knew whether or not the person being examined worked in vinyl chloride.

Dr H Falk replied that none of the clinical examiners were aware of the occupational status of the workers at the time of the examination.

Dr R I McCallum (*University of Newcastle upon Tyne*) asked Dr Falk to give in more detail the way in which histological diagnosis was made in the case of lung cancer shown in his slide. Was this done by one individual or by a panel of pathologists? How were the specimens of tissue obtained: by biopsy, surgical resection or at autopsy? It was remarkable that in none of the cases was an oat cell carcinoma diagnosed, as this was the type often considered a characteristic result of exposure to a chemical carcinogen.

Dr H Falk replied that the WHO lung cancer classification scheme of Kreyberg (1967) was used. Four pathologists reviewed the slides and agreed on the interpretation (Dr Louis B Thomas and Dr T Powell, National Institutes of Health; Dr M Kuschner, State University of New York; and Dr Laszlo Makk, St Anthony Hospital, Louisville, Kentucky). All available pathological material for each case was reviewed.

The expanded pathological review currently underway would include the selection of multiple control cases of lung cancer from the same hospitals (with similar age and date of diagnosis to the study cases) and a blind review by a panel of pathologists in a more detailed evaluation of available pathology material.

To Dr Falk's knowledge large cell undifferentiated carcinoma of the lung had not been related to exposure to chemical carcinogens, which made the findings in the VC cohort even more intriguing.

Dr A J Fox (*Employment Medical Advisory Service, London*) asked how many factories had been studied individually in the USA. What proportion of these had indicated vinyl-chloride-associated disease?

Dr H Falk replied that cases of hepatic angiosarcoma had been seen at 5 of the 8 PVC polymerization plants opened prior to 1950.

There was some confusion in this area in that a number of the VC worker mortality studies had been overlapping. Three separate studies, for example, (the NIOSH-CDC study, the Tabershaw study, and the Monson-Peters study) had all looked at the Louisville, Kentucky plant where the initial angiosarcoma cases occurred as well as at a varying number of additional plants. Compounding the problem was the fact that the definitions for entrance into the cohorts studied differed from study to study, so that the results even at the same plant were not identical.

Dr J A Bonnell (*Central Electricity Generating Board*) asked whether, since vinyl chloride monomer was a carcinogenic agent, there was any evidence in experimental animals or in human clinical experience that the skeletal or skin changes described might be premalignant conditions.

Dr H Falk said that cases of angiosarcoma in the USA did not have a history of acro-osteolysis or skin problems, although they did not have the multiple tests for early changes of acro-osteolysis. It would seem, therefore, that the skin changes were not premalignant conditions.

Professor I J Selikoff (*Mount Sinai School of Medicine, City University of New York*) said that a review of known details of identified cases of vinyl-chloride-associated angiosarcoma of the liver by Dr Lloyd (1975) of the National Institute for Occupational Safety and Health had demonstrated that the median duration from onset of exposure was approximately seventeen years. These cases were derived from the rather small number of polymerization workers employed during the establishment and initial growth of the vinyl chloride industry. Attempts were underway to identify and trace the initial groups of workers, employed during the years 1938-55, since analysis of their experience would allow evaluation of the risks which might be suffered by the very much larger group of vinyl chloride workers exposed more recently, in a period during which PVC production was increasing at the rate of approximately 10% per annum.

Limited data bearing on the problem had been obtained. In one polymerization process studied, 257 men had been employed for five years or more in the period between 1946, when the plant opened, and 1964. Each man had been traced to 1 July 1974, with 25 deaths from all causes: 3 of the deaths were due to angiosarcoma of the liver (Nicholson *et al.* 1975), each confirmed on review of autopsy material (Thomas & Popper 1975); in addition there was one death due to ruptured oesophageal varices. Another worker, examined during the clinical survey at this facility (Lilis *et al.* 1975) had had a successful porta-caval shunt operation for the same condition. These experiences suggested that vinyl-chloride-associated disease would be an important hazard for vinyl chloride workers in the future, unless control of exposure resulted in at least some reversal of the risk.

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