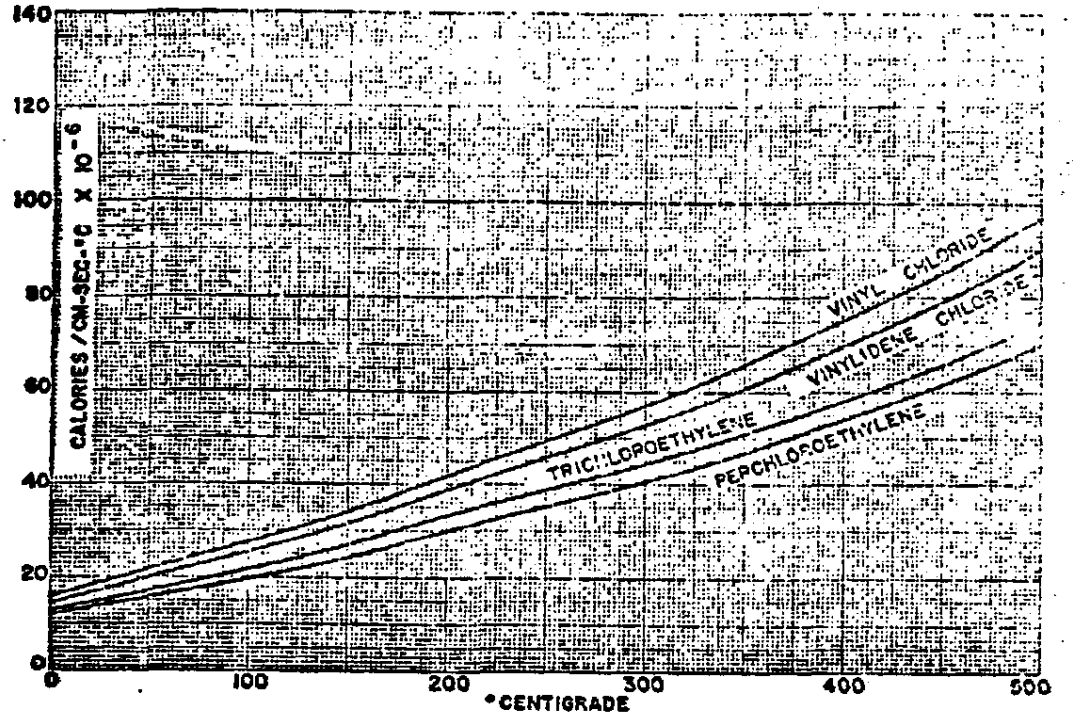

Figure 6-11. Vapor thermal conductivity from 0° C to +500° C.

no literature data and so its surface tension at 20° C was calculated by the equation

$$\sigma = \left(\frac{[P]\rho}{M}\right)^4$$

where

σ = surface tension at 20° C
$[P]$ = Parachor, estimated from the molecular structure
ρ = liquid density at 20° C
M = molecular weight

The anticipated error by this method is 3-5 percent. The data for all four compounds were extrapolated over a wide temperature range by Kharbanda's nomograph of

$$\sigma_2 = \sigma_1 \left(\frac{T_c - T_2}{T_c - T_1}\right)^{1.2}$$

where

σ = surface tension at temperature T
T_c = critical temperature

The accuracy for this estimation method is very good, averaging 1-2 percent error.

Thermal Conductivity. There are no experimental data for either the vapor or liquid thermal conductivity of vinyl chloride or vinylidene chloride. Mason[10] has experimentally determined the liquid thermal conductivity and his data appear to be more reliable than the earlier reported data.[1,4] McGovern presents the vapor thermal conductivity of trichloroethylene and perchloroethylene but the estimation method used is not very reliable. None of the present estimation methods gave a reasonable temperature-thermal conductivity trend for the vapor phase. Hence, only the liquid thermal conductivity is presented here, and then only for the experimentally determined trichloroethylene and perchloroethylene since estimation methods gave highly unreliable results for the liquid phase also.

Vapor Thermal Conductivity. The vapor thermal conductivities have been estimated by the method of Owens and Thodos[11], with an expected error of ±5%.

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4. "Vinyl Chloride Product Bulletin," The Dow Chemical Co., Midland, Mich. (1954).

AP00007605

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Plastics Division

file 652

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Dr K A Hochschwender
Director, Public Affairs
American Hoechst Corporation
Route 202-206 North
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USA

CC: Dr R Adams - Air Products
Mr R Harding - Society of Plastics Industry

Mayo - Did all of the Angios in the USA originate in plants that manufactured emulsion using certain surfactants in their mixes?

RECEIVED
JAN 24 1977
A. ROSS ADAMS

Your ref.	Our ref	Tel ext	Date
	JS/KEW/DSO-107	3162	9 December 1976 (Dict 8 December)

Dear Karl Roo

DR J C WAGNER - PVC DUST

I tried to get in touch with you today to follow up my letter of 16 November concerning Dr J C Wagner of our Medical Research Council Pneumoconiosis Unit and his work on PVC dust. So far as I know, Dr Wagners work has not been published in 'Nature' but the publication could be imminent. ARA

Dr Wagner was in the USA last week I believe and I have not heard of any repercussions. However, I have today had news of a disclosure he has made at a semi private colloquium on toxicological and environmental problems being held in Luxembourg on 7,8 and 9 December. During a discussion of a paper by Dr Hans Popper on the effect of toxic materials on the liver, Dr Wagner gave an account of his work with PVC powder. Our informant tells us that the report was given in a lurid dramatic sensational way calculated to cause the maximum amount of worry and alarm. Some delegates were not taken in however, and commented that it was deplorable that research results should be presented in such an ill digested manner, but Dr Wagner took the view that he was a simple researcher who was reporting findings and it was up to others to interpret his work!

We have been privileged to have confidential discussions with Dr Wagner in this country on 9 November and to have access to the draft letter he was proposing to publish in 'Nature'. Dr Wagner had made us well aware that he expected us to respect the confidentiality of his draft submission to 'Nature' and up to now we have done just as he wished. However, his disclosure in this Luxembourg meeting has changed things quite substantially. We felt that we could talk with our government Health and Safety Executive and Medical Advisory Services today concerning his work and we are sending them appropriate documentation. For your information, we enclose a copy of a draft precautionary brief we have drawn up for our own management and PR people.

..../..

3) paste polymer to carry out a feasibility study for an inhalation experiment.

In addition it would seem advisable to supply the unwashed and washed ICI product for 1) and 2) and to consider whether the products of both firms need to be investigated by inhalation. Dr. Wagner should, if possible, be persuaded to accept the specimens coded so that he is unaware of their origin and whether or not they have been washed. It would probably also be best if he was unaware of the origin of the powder he uses for his inhalation experiment.

In relation to c) findings in other studies may be of great importance. In an investigation carried out in a similar way to the PVC study, Dr. Wagner found that a high percentage of rats receiving crystalline silica developed a reticuloendothelial tumours. Most of these were composed of malignant histiocytes, many of which in the early stages appeared localised as reticulum cell sarcomas. The description of the tumours in silica-treated animals is somewhat similar to that found in the PVC treated animals; clearly full pathological examination of the animals already dead and of further animals will need to be completed before comparisons can be properly made. There is, of course, ample evidence that silica is not a carcinogenic hazard to man.

There is well documented evidence that inplantation of millipore filters or I.P. injection of mineral oils can produce tumours of the lympho-reticular type in mice. For example, medicinal quality oil when injected into BALB/C mice can induce, as well as granulomatous nodules, myelomonocytic leuknemia. The formation of plasma cell tumours has also been described. . DBA/2 and CBA mice also develop reticulosarcomatous tumours and leukaemia with this treatment. These experiments suggest that in mice and rats reticulosarcomata may develop secondarily from granulomatous type lesions.

The effect on the rat of particulate matter and tissue-damaging chemicals (including surfactants) when injected subcutaneously has been studied in great detail by Golberg and Grasso. There is little doubt that many such substances which are not a carcinogenic hazard to man do produce a sarcomatous reaction in the rat, this reaction being dependent on the physico-chemical properties rather than the inate carcinogenic property of the materials. It might be that PVC with a strongly held coating of surfactant could behave in a similar way as a "secondary" carcinogen rather than a primary carcinogen. In other words the development of the tumours may be secondary to the formation of a primary lesion which is either unlikely to be produced in man or, if it is produced, will not necessarily lead on to cancer induction.

This possibility is well worth further study since Wagner's findings might at present be taken as indicative that PVC is causing reticulum cell sarcomas. Evidence on the mechanism by which the lesion develops in rats may be essential in the interpretation of his findings. The need for a suitable programme of work should be discussed by the scientists of the CIA. The desirability of someone other than Wagner carrying out the studies should also be considered. The person probably the most interested in this field in the UK is Dr. Paul Grasso of BIBRA.

The need for the radioactive tracer study suggested by Wagner should be given careful consideration. Particles will almost certainly

Continued...

enter the body when given by inhalation since they will probably be swallowed and taken into the gut (by persorption). From the gut they could travel to the liver. It is doubtful whether the study will be helpful in answering the main question, which is what the development of reticulum cell sarcomas might mean to man.

The need was discussed at the meeting for the occupational histories of those who have developed angiosarcoma attributable to vinyl chloride to be re-examined to see whether or not evidence exists of a relationship of tumour incidents with exposure to paste polymer. It is probable that this has already been looked into.

Consideration should also be given to the need to formulate a scientifically based reply to Wagner's letter to "Nature".

M. Sharratt
(Dictated but not signed by
Dr. Sharratt)

Dahm(a)/Dahm.4(a)/(b) - MS/BAJ
23rd November 1976.

AP00007608

3rd DRAFT

CONFIDENTIAL

IMPERIAL CHEMICAL INDUSTRIES LIMITED
PLASTICS DIVISION

PRECAUTIONARY BRIEF RELATING TO PROPOSED LETTER TO 'NATURE' BY DR J C WAGNER

1. Introduction

Since the discovery 3 years ago that the rare cancer, angiosarcoma of the liver could be caused in man by exposure for long periods (normally more than 10 years) to high levels of vinyl chloride monomer (probably well in excess of 500 ppm), a great deal of attention has been paid to occupational health in the PVC industry. In particular great advances have been made in improving factory hygiene and reducing exposures to VCM. A tripartite working group consisting of Government, Unions and Industry drew up an Interim Code of Practice for handling VCM based on exposure to 25 ppm over a time weighted average of 8 hours. This Code of Practice was modified in November 1975 to require an 8 hour personal TWA exposure of 10 ppm with which the industry is complying.

Careful medical screening and epidemiological surveys have discovered around 55 VCM related angiosarcoma cases in the World, two of which were in the UK. In almost every authenticated case of angiosarcoma, the victim had been an autoclave cleaner; it is in this area that, the greatest advances have been made in minimising the health hazard.

2. Dr Wagner's Proposed Letter to 'Nature'

A copy of this letter is appended. Dr Wagner gives a factual report of work he has done on one sample of PVC powder, a paste polymer. In laymen's terms he injected a suspension of PVC particles into the cavity between the lung's external covering and the rib cage in rats. About 1 year later (half the normal lifespan of a rat) four of the animals died. The animals had tumours mainly

..../..

AP00007609

associated with the liver but these were not liver angiosarcomas caused by VCM. As Dr Wagner says this is a preliminary report - 44 other rats are still under observation. His.letter is mainly concerned with identification of the various tumours he has found in the 4 dead rats.

Dr Wagner makes no comment to link the development of the tumours with VCM in the PVC particles and indeed (we repeat) the tumours are not the liver angiosarcomas typically related to VCM. The paper represents one portion of an overall programme Dr Wagner has been pursuing. Using another type of commonly inhaled, fine dust which has not been associated with cancer in man he has discovered that somewhat similar tumours can be induced by this unnatural process of injecting into the pleural cavity. Such a mode of entry into man in any manufacturing process is inconceivable. This is no criticism of Dr Wagner's work which is presumably aimed at studying carcinogenesis in the reticulo-endothelial system, the body's scavenging mechanism which involves among other things the generation of white blood cells and the removal of foreign bodies.

3. Questions and Answers

Q1 What is new about Dr Wagner's work?

A1 This work involves the introduction of a suspension of dust into the pleural cavity, a normally inaccessible area between the lung's external covering and the rib cage.

Q2 What is he trying to prove?

A2 Dr Wagner works for the MRC Pneumoconiosis Unit in South Wales. He is examining the possibility that different types of industrial dust might have cancer causing properties; this work follows a number of studies he has carried out on asbestos. He has found it possible to administer in one injection as much dust as can be inhaled by the rat in several years. He recognises that the route of administration is abnormal and

..../..

that positive results in his tests will need to be investigated before their relevance to man can be established.

Q3 Have any of these other dusts given rise to the same effects as stated in the article?

A3 The work is in an early stage but we believe that Dr Wagner has had similar results from other dusts not associated with cancer formation in man.

Q4 What is the significance of Dr Wagner's discovery?

A4 The research is novel and the significance of the initial results is still being discussed by doctors and others.

Q5 How does this development affect PVC manufacture?

A5 We believe not at all. All operators wear dust masks where they carry out jobs in areas where dust occurs. This is a standard precaution adopted by the industry over many years. PVC dust is classed as a 'nuisance' dust, ie it does not produce a significant toxic effect.

Q6 What further precautions will you institute?

A6 We believe we have adequate protection but industry is interested in anything in Dr Wagner's work that might lead to further improvements in hygiene standards.

Q7 This is a fine polymer - is it paste polymer?

A7 Yes but we understand that Dr Wagner's future work will embrace a range of PVC paste powders.

..../..

Q8 You say that the full significance of the work has yet to be assessed by doctors and that the research is still in its early stages; supposing worst fears materialise? How could this then change the situation?

A8 In the UK, the CIA and Employment Medical Advisory Service health survey of the PVC industry in 1975 showed no excess disease or mortality of PVC workers against the general pattern of the population other than the two known cases of angiosarcoma.

JS/CJH/DSO-107
6 December 1976

(for NATURE) Copy for CIA VC Chee +2 18/11/76

The production of sarcomas following the intrapleural inoculation of fine particles of ~~polymerised~~ vinyl chloride.

Poly Vinyl chloride particles of the finest commercial grade, mean particle diameter 0.508μm (range 0.07 - 1.56μm) were introduced into the pleural cavity of six-week old Cesarean derived Wistar rats of the ICI Alderley Park strain. The particles were suspended in physiological saline and introduced into the right pleural cavity using the method described by Wagner and Berry, (1969). 48 animals were inoculated, 24 of each sex, in August, 1975.

This is a preliminary report on the first four animals that have died up until the 1st November, 1976.

The first animal developed a large fibroadenoma of the breast, which was causing discomfort, and was killed in July, 1976. Histological examination of the liver showed the presence of enlarged hyperplastic Kupffer cells in the liver and hyperplastic histiocytes in the spleen.

The second animal died of pyelonephritis in July, 1976, the liver was slightly enlarged, pale in colour, and the spleen was grossly enlarged and firm in consistency. Sections from the liver showed the presence of clumps atypical histiocytes, some with bizarre nuclei. Sections from the spleen demonstrated that the normal architecture is maintained, "T" dependent lymphocytes appear to be normal. No secondary germinal centres are seen - the marginal zone is indistinct and merges into the red pulp. The cells in the red pulp are large with clear cytoplasm. Nuclei and cells vary in size and shape. There are more multinucleated cells than usual and occasional nucleated red blood cells are seen. In addition, there are collections of small deeply stained cells, these may be artefact but the possibility of monocytic cloning should be considered.

AP00007613

The third animal was found dead on the 10th October, 1976. The liver was grossly enlarged and pale with obvious yellow tumour nodules extending throughout the liver substance. The spleen was grossly enlarged and firm. The liver sections showed the normal hepatic cells to be replaced by a tumour consisting mainly of reticulum-like cells with occasional foci of grossly atypical histiocytic cells. The spleen was similar in appearance to that seen in the previous animal. The atypical cells in the red pulp were clearly malignant giving the appearance of a tumour arising in situ.

All three animals had small white granulomata at the site of inoculation and scattered through the right chest cavity with prominent nodules on the diaphragm.

The fourth animal showed malignant histiocytic tumour nodules in the right pleural cavity, lung, spleen and bone-marrow, with occasional foci of grossly atypical histiocytes in the sinusoids of the liver.

J. C. Wagner MD. FRC.Path

MRC. Pneumoconiosis Unit,
Llandough Hospital,
Penarth,
S. Glamorgan.
CF6 1XW

Reference

Wagner, J.C., and Berry, G., Brit. J. Cancer, 23, 567-581, (1969).

AP00007614

This contains the draft of the proposed letter by Wagner to 'Nature'. Would you please be careful what you do with this draft letter so that we do not cause any offence to Dr Wagner. It would be better if he achieved his ambition of having it published first in 'Nature'. We think it is important that you should have this information because I am pretty sure that Dr Popper will be reporting these very preliminary and premature results to your government on his return.

May I say that we in ICI have done some "in vitro" and "in vivo" work on PVC powders. The "in vitro" work has been completed and was the subject of a paper to the American Chemical Society last spring by Dr Piggott of our Central Toxicological Laboratory. Dr Piggott is still doing his "in vivo" work which involves the injection of PVC powders into the trachea and peritoneal cavity of, I believe, rats. So far, no abnormal reactions of the histiocytes in liver or spleen has been observed, but the total duration of Dr Piggott's work is nearly six months compared with the one year plus in Dr Wagner's work. The CTL work has, therefore, little bearing on Wagner's results except to indicate the need for Wagner to do further work to determine which components of the emulsion paste are responsible for the effects he has observed. There is also the need to investigate whether materials administered via the lungs are capable of producing such reactions, since only this route has any relevance to possible industrial exposures. In other words, Dr Wagner has some interesting data but we have a long way to go in interpreting the very preliminary findings in his work. I would hope that our scientific community will take the news calmly and logically and not jump to any premature conclusions. If I can be of any help in elucidating anything further, please do not hesitate to get in touch with me.

With best wishes.

Yours sincerely

J Stafford
Division Manager
Health & Environment Protection

PS: I also enclose a copy of the draft CIA report of our 9 November meeting with Dr Wagner. Ross and Ralph have been given copies of your letter.

DRAFT

CONFIDENTIAL

Report of a Meeting Between Representatives of the CIA and the MRC Pneumoconiosis Unit, held at Llandough Hospital on 9.11.76, to discuss recent findings on BP Paste Polymers, and suggestions for action by the CIA

Those present were:

Dr. P. Elmes
Dr. P. Smith
Dr. J. C. Wagner
and a number of Dr. Wagner's team from the MRC
and Dr. C. H. B. Binns (BP)
Dr. G. Piggott (ICI)
Dr. M. Sharratt (BP)
Mr. C. H. Thompson (BP)
Dr. D. M. J. Williams (BP)

Please add consistin resins not suspension resins

The meeting had been suggested because Dr. Wagner's recent findings had added a further dimension to the vinyl chloride/PVC problem. Dr. Wagner began his studies on the effects of PVC particles injected into the right pleural cavity (the space between the chest wall and the lungs) of rats some time ago. The first experiment was discontinued because of infection in the animals and the present experiment was started in August 1975. He has injected 20 mg of BP B130/1 polymer into the pleural cavity of 24 male and 24 female Wistar rats originating from the ICI laboratories at Alderley Park. The particle size of the polymer ranges from 0.07 to 1.56 microns with a mean of 0.508 microns (determined by EM). Surfactant on the surface of the particles is moderately stable, being removed by alcohol but not by water washing.

To date, five of Dr. Wagner's rats have died or have been killed. The findings on four are to be described in a letter which the MRC hope will be published in "Nature" within the next month or so. Briefly, the changes described by Dr. Wagner in the five rats were:

1. Killed because of breast cancer (a common finding in these rats) but the liver showed the presence of "enlarged hyperplastic Kupffer cells" and the spleen "hyperplastic histiocytes".

2. Died with kidney diease (again a common abnormality) but the liver contained "clumps of atypical histiocytes, with some bizarre nuclei". Abnormal cells of uncertain origin were present in the spleen.

3. Died. The liver cells were largely "replaced by tumour consisting of reticulum-like cells with occasional foci of grossly atypical histiocytic cells". The spleen was similar to that in animal 2 but the cells in the red pulp "were clearly malignant, giving the appearance of a tumour arising in situ".

4. "Malignant histiocytic tumour nodules in the right pleural cavity, lung, spleen and bone marrow and occasional foci of grossly atypical histiocytes in the sinusoids of the liver".

5. Rat examined only recently. Smears showed a "monocytic leuknemic type of picture".

All rats have small granulomata in the chest cavity.

Dr. Piggott described ICI's findings with a similar type of polymer. Polymer with a surfactant coating could kill macrophages (cells which take up particles in the body) when cultures of the cells were in contact with them. Silica and asbestos also kill macrophages while many "nuisance" dusts do not. However, when the polymer was washed free of surfactant it was no longer harmful to the cells. In rats receiving the ICI polymer via the trachea, only minimal fibrosis was seen; these rats were not kept long enough to demonstrate that by this route a Wagner-type reaction did not occur.

Dr. Wagner is concerned that inhaled particles of PVC dust might be taken up by the tissues, transported to the liver and produce a reaction in man similar to that which he has found in rats. One of his interests is in the mechanism by which the polymer particles move around the body. He has, as yet, no direct evidence that PVC particles move from the chest cavity but, by analogy with the behaviour of silica particles, he feels it reasonable to assume that they do. He considers it possible that the particles migrate through the "bare area" of the liver (the part of the liver immediately in contact with the diaphragm) to the blood vessels of the liver where they are taken up by specialised cells (most likely the Kupffer or similar cells) which then, presumably on becoming malignant, pass to other parts of the body.

Dr. Wagner would like to repeat his study using paste polymer and alcohol-washed polymer. He would be willing to introduce fine (cosmetic grade) talc as a control since this produces fibrosis (the granulomata in the chest) but not cancer (in man). He would also like some polymer to investigate the feasibility of producing dust clouds suitable for a long-term rat inhalation experiment. He suggested that industry might consider approaching Harwell to carry out studies on the migration of PVC coated radioactive iodine particles into the body; this he felt would answer quickly whether or not PVC particles could enter the body tissues following inhalation; the same material could, of course, be used to trace particles from the chest and so would be useful to Dr. Wagner in investigating his theory of particle migration.

The CIA's concern will be not so much with the theory of mechanisms of particle transport as with the relevance of the findings to man. Three aspects are of interst:

a) do PVC particles of the size found in paste polymers enter the tissues in significant quantities when inhaled (and therefore ingested)?

b) does the surfactant coating play any role?

c) if particles do enter the tissues will a similar response to that in rats occur in man?

In relation to a) and b) it would seem reasonable for the CIA to provide the samples requested by Dr. Wagner, that is

1) paste polymer as previously tested

2) alcohol-washed paste polymer - preferably giving a negative macrophage response

Continued...

Route J. T. Barr / L. B. Tepper / A. R. Adams

IMPERIAL CHEMICAL INDUSTRIES LIMITED
PLASTICS DIVISION

7/10 Wmk (Last)

TO: SPI VINYL SUBCOMMITTEE
FROM: W R SORENSON/W D DAVIS
JUNE 28, 1978

PAPER FOR EMAS MEETING, 5 MAY 1978 AT REGINA HOUSE

RECEIVED
RESEARCH & DEVELOPMENT
JUL 5 1978

PVC DUST

W. M. SMITH

1 Summary Note on Meeting with MRC Pneumoconiosis Research Unit 31 January 1978

Introduction

Under CIA auspices, a meeting was held on 31 January 1978 with HSE, EMAS, DHSS, TUC, BIBRA and CIA representatives present to discuss the MRC work on PVC dust. The following points arose.

(a) Dr Wagner of the MRC in August 1975 gave 48 rats a single intra pleural injection of 20 mgm of PVC emulsion polymer in saline. Between 12 and 18 months, 9 animals died and of these 5 had liver tumours. Pathologists agree 3 tumours were malignant, arising from Kupffer cells. One tumour occurred at the injection site. Nothing further was found until rats 33-45 died and showed liver and spleen fibroses and Kupffer cell damage. 3 animals still survive.

(b) In January 1977, Dr Wagner exposed 48 rats to inhale an atmosphere containing 12 mg/m^3 PVC emulsion polymer dust for 7 hrs day/5 days week for 5 months. In June 1977, 6 exposed rats were sacrificed and evidence found of dust deposition in macrophages in the alveoli, lung tissue, liver and spleen. In January 1976, a further 6 rats were sacrificed and found to have interstitial fibrosis and multiple granulomata in lungs, aggregates of dust around splenic vessels and occasional particles in Kupffer cells in the liver.

(c) In post mortem examinations of human cases in the Llandough Hospital, Dr Wagner found PVC particles in lungs and liver of a man who died from Kupffer cell sarcoma, PVC in the liver of a man who died from a liver tumour, PVC particles in liver and spleen (and interstitial fibrosis) in a man who died from bleeding oesophagal varices and PVC particles in lungs and spleen of a South Wales factory employee who died of bronchitis and emphysema.

(d) Dr Pigott of ICI's CTL described in vitro and in vivo experiments with PVC powders. In vitro, emulsion polymers were cytotoxic when some specific surfactants were left on the particles' surface. Intraperitoneal and intratracheal injection of emulsion polymers into animals showed no response after 6 months. Dr Pigott concluded the PVC powders he had tested in this way were unlikely to produce fibrosis in man.

(e) Dr Elmes and Dr Wagner thought it was too early for Dr Pigott to draw such a conclusion. Moreover there was scattered clinical evidence in the literature to support the possibility that PVC dust may be fibrogenic but Dr Elmes agreed an epidemiological survey would be required to prove this. All agreed that such a survey could not be warranted on the basis of the present evidence.