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IMPERIAL CHEMICAL INDUSTRIES LIMITED
PLASTICS DIVISION

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NOTE FOR APME VCM COMMITTEE MEETING, LONDON 27 FEBRUARY 1979

PVC DUST

I hope this note will bring you up to date on what is happening on PVC dust in the UK.

1 Tripartite Medical Meeting 24 January 1979

So far as PVC dust is concerned, this was a much happier meeting than we have had for 1/2 years because the Health and Safety Executive (HSE) and in particular its Employment Medical Advisory Service (EMAS) were satisfied that industry is giving serious attention to PVC dust. Industry may not yet be doing everything HSE would like to see us do but we have made a start. Work already initiated was reviewed and possible further work programmes were discussed as follows.

2 Literature Survey

Dr Greenberg of EMAS tabled the attached paper Appendix 1 noting work reported since we had met in May 1978. He included a personal communication from Dr Burrows of ICI on a survey of workers in an ICI PVC Fabrication unit - regrettably this paper has not been accepted for publication because of defects in its protocol. This contrasts strangely with the ease with which Mapp et al and others of our antagonists can publish. EMAS and HSE continue to note that industry has not been able to disprove that long term inhalation of PVC dust is harmful to man.

Dr Pigott of ICI's Central Toxicology Laboratory has had a literature search done on PVC dust. We have pruned the list because it contain d so much marginal material and we hope to have something better available soon.

3 Survey of PVC Dust Exposed Employees at ICI's Hillhouse Works

When Dr W G F Adams reviewed the work we had done in 1975/6 on ICI's Hillhouse employees examined by the National Coal Board's Radiographic Unit, he found that he could not write a paper acceptable to a scientific j urnal because of lack of adequate control populations. Having met a somewhat similar problem in Dr Burrows' study and still being criticised by th HSE that we commented adversely on already published papers but published nothing ourselves, ICI have asked an independent body, the Institute of Occupational Medicine (IOM) in Edinburgh to carry out a survey which could and would be published. This work is now under way. The IOM are surveying 750 people out of a 2,400 population who have been at s me time employed at Hillhouse in the period since 1 January 1967. The IOM hav been given a free hand in choice of exposed and unexposed, present and former employees. In addition to full chest x-rays, spirometry, gas transfer tests etc, the IOM's industrial hygiene team will survey environmental conditions in the plant. The IOM are free to publish their survey in the medical and scientific press and indeed ICI will expect them to d (so. [illegible] Already there are some criticisms emerging about sampling/selection f people for inclusion in the survey. Regrettably the IOM could not d vote the resources to examine the total population. The entire matter f sampling/selection has been left to the IOM and has not been influenced

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by ICI. It is hoped that the survey will be reported by mid-year though it may take longer than this to get into journals.

We would plead that other companies who have done regular studies of their PVC dust exposed populations should publish their findings. If you have negative information, it is worth publishing!!

4 Improvement in PVC Dust Hygiene

At some PVC plants, capital expenditure has been authorised to impr v dust hygiene and HSE are pressing us for details of results of monitoring in our plants. Visits by HSE and EMAS personnel have been made to mulsion PVC plants in particular to familiarise themselves with processes and conditions. They seem however more concerned about conditions in custom rs' premises and were pleased that the UK PVC producers have now revised their literature to re-emphasise to customers the need for care in handling PVC dust and for keeping as far as possible below 10 mg/m^3. Though th y did not say so explicitly, we believe that the survey they had asked the Medical Research Council's (MRC) Pneumoconiosis Research Unit (PRU) t carry out at a customer's premises had not revealed any respiratory disorders despite allegedly high PVC emulsion dust concentrations in th working atmosphere. The survey was led by Dr J C Wagner himself who is reputed to take the view that the exposures had not been long en ugh t show any physiological effect.

5 Animal Studies

[redacted]

The UK PVC industry is divided on its view about the value of a dust inhalation study on animals. The cost would be at least £500,000 for an inhalation experiment and in ICI's experience the technical difficulties would be enormous. Moreover the choice of which "PVC Dust or Dusts" would be far from easy when one considers the differing particle sizes, surfactant coatings etc; our critics would say that Product XYZ proved to be all right but Product W with a different surface area/structure might not! After 3 years work and £0.5m expenditure, we could be left with an equivocal result which would overshadow even the most negative findings in an epidemiological survey. The question arises whether this money would be better spent in improving works hygiene.

The HSE are still clearly of the view that further animal work is required here (but it is of interest to note their very firm view that enough animals had been sacrificed on VCM toxicity work). Some UK companies are in favour since this could be one way of rebutting Wagner's claims for his own work which he has not yet published in full and als it would obviate the criticism that industry experiments on humans rather than animals. In addition to the technical difficulties of the inhalation experiment, there are some cogent arguments against the need for inhalation experiments.

(a) Only one alleged pneumoconiosis case has been reported in any detail (Arnaud).

(b) Many companies have x-rayed employees regularly and found no cases of pneumoconiosis. Selikoff has x-rayed many US PVC workers and found no cases.

(c) In the UK, suspected cases are referred to Pneumoconiosis Medical Panels - none attributable to PVC have been reported to our knowledge.

(d) Short term tests at ICI's CTL have not indicated fibrosis.

(e) The NIOSH work on inhalation exposure of Geon 121 to monkeys, guinea pigs and rats gave no evidence of fibrosis. NIOSH say the exp rim nt was designed to test for fibrosis - they don't know how they would overcome the problems of design of such an experiment to test for carcinogenicity and indeed they say they would undertake such a study only if human epidemiology gave an equivocal result.

(f) On the subject of carcinogenicity, Wagner's work on rats does not appear to indicate such an effect and neither Waxweiler nor any other epidemiologist has yet produced a well accepted study in this area.

The UK industry is coming round to the view that they should ask a small group of experts to construct a protocol for a PVC Dust InhalationStudy to demonstrate whether PVC dust is carcinogenic and/or fibrogenic. The exercise of composing the protocol may help in deciding whether the study is practicable. This group has also proposed a protocol for studies to assess the validity of the intrapleural injection technique as a method for testing carcinogenicity of particulate matter but no decisions have yet been made whether to commission such a study or if we do, how widely to cast around "dusty" industries for financial support.

6 Epidemiological Studies

Like ourselves, the HSE have tried to have a dialogue with Waxweiler post-Dubrovnik but failed. Everyone seemed to be agreed that Waxweiler had done an interesting but complex piece of work which deserves further study by people competent to do so. The HSE epidemiologists would like to try out the Waxweiler approach as another potential tool. They proposed a mortality study of workers exposed to PVC dust in the UK - this would be a natural extension of the VCM study done in 1974/5. However the mixed exposure to VCM and PVC dust could be difficult to disentangle in job histories. HSE were adamant that a survey in PVC fabrication workers would be even more difficult. A small group of Government/industry biostatisticians will meet to discuss the feasibility of such a study. The HSE seem keen to do it but some industry representatives doubted whether the vast amount of work involved could be justified. (If it avoided a whole-life inhalation study on rats it could be a worthwhile venture!)

In July 1978 we found from Ethyl Corporation that Dr Patricia A Buffler of University of Texas would be publishing a paper which alleged an xcess of respiratory tumours in PVC workers. Though Dr Torkelson of Dow has asked that I should be given a pre-print, this has not yet been received. HSE didn't know Dr Buffler or of her work. However she is known to ICI's Dr Paddle who hopes he may meet her this month at Stanford.

7 Medical Research Council and University Research

Dr Wagner of the MRC has been provided with samples of washed and unwashed emulsion PVC powders for his animal work. (Some samples have been washed to remove surfactants.) The samples are from BP and ICI but hav been supplied under Chemical Industry Association (CIA) Code Numbers. Th MRC claim that they can distinguish between the CIA codes and tell whose material they are examining! Dr Wagner and his Director, Dr Elmes, hav visited ICI's plants and expressed disappointment that they had not been commissioned to carry out the Hillhouse study.

Dr Wagner does not disclose much about the progress of his own animal work where he must either be finding zero results or encountering pr bl ms he won't admit to us. Oddly enough in Appendix 1 Dr Greenberg does not refer to the paper Dr Wagner gave to the Pathological Society of Great Britain and Ireland in Southampton on 5 July 1978. The synopsis of the paper was as follows:-

" THE BIOLOGICAL EFFECTS FROM FINE POLYVINYL CHLORIDE PARTICLES

J C Wagner

MRC Pneumoconiosis Unit, Llandough Hospital, Penarth

Attention has been focussed, both in man and experimental animals, on the effects of inhalation of the gas monomer, vinyl chloride. Recently, note is being taken of the possible effects of the inhalation of the polymer in man. The particl s in question are those produced commercially as 'paste polymer', having an average diameter of 0.15 microns, and accounting for more than 10% of the production in Britain. There are now strict regulations for the control of the monomer gas, but the particles are regarded as nuisance dust and their emission is not covered by specific legislation.

Our studies on rats where both inhalation and implantation m thods of exposure have been used, and examination of tissue from human cases exposed to 'paste polymers', indicate that these small particles are not as benign as has been supposed. Techniques have been developed by which these particles can be demonstrated in ordinary histological preparations, and by transmission electronmicroscopy. "

This is a fairly guarded statement which didn't attract any attention.

The CIA samples mentioned above will be used by Dr Wagner in injecti n (presumably intra-pleural) experiments early 1979. He would like t d more PVC dust inhalation studies and it is rumoured that he is trying t get a university team (with no previous inhalation experience!) involved. Clearly progress is slow and this could in large part be related t th immense methodological problems in this area. My own layman's view is that Wagner seems to be trying to correlate intra-pleural or intra-trach al injection with inhalation and set up say IP injection as a quicker, cheaper test for carcinogenicity of particulates.

The CIA are doing everything possible to provide Wagner and university researchers with materials and information. Is there any comparabl activity going on in European universities or research institutes?

8 Italian Epidemiological Study

It is interesting that neither the HSE nor the Trade Union Congr ss Medical Adviser is pressing us for an explanation of Foa et al or Mapp et al papers. Like ourselves, they seem to have concluded that if there had in fact been so many PVC attributable pneumoconiosis cases in Italy, we would have had much more informati n from the Italian companies conc rned and the press/scientific literature would have publicised th cases.

9 PVC Staining Technique

Some time ago my colleagues Pigott and Wilson in our Central Toxicology Laboratory developed a staining technique for PVC particles. This t chnique has been made available to Wagner, Arnaud, Dr Torkelson of Dow and more recently to Dr Kammuller to be given to CIVO. We hope this technique will be subject of a paper in the Journal of Stain Technology and prove useful in identifying PVC particles in path slides.

J Stafford

Circulation

APME VCM Committee
UK CIA VCM Committee
PVC Dust file
JS (10)
Mr G J Sleddon
Dr B Bennett, Hillhouse
Dr F W Best, Millbank
[redacted]
Dr T R Torkelson, Dow
Dr W Davis, Goodyear
Mr R N Wheeler, UCC
Dr M N Johnson, BFG
Mr A G Wheeler
Dr J Conbere ICI Americas
Mr M J S Gibbons

JS/MJE/DSO-107
6 February 1979

Appendix 1

PULMONARY DISEASE IN THE VCM/PVC INDUSTRIES

Some Further Reports Studied Since May 1979

Some Biochemical and Histopathological Changes Induced by PVC Dust /Geon-121/in Rat Lung. Agarwal, D.K. et al (1978). Environmental Research, 16, 333-314.

"Enzymatic and pathomorphologic alterations in rat lungs were studied at different time intervals up to 180 days after a single intratracheal administration of 25 mg of polyvinylchloride dust. The activities of two energy-linked enzymes, succinic dehydrogenase (SDH) and adenosine triphosphatase (ATPase), and three lysosomal enzymes, acid phosphatase, glucuronidase, and ribonuclease, were significantly increased in the early period and then started to decline. The activities of SDH and ATPase reached control values at 150 days, while those of the lysosomal enzymes remained significantly higher up to this period. Histopathologically, the pulmonary response was in the form of acute inflammatory changes during the early stages of dust burden, followed by the development of granulomatous lesions containing small amounts of stromal elements."

No significant difference was stated to have been observed in the rate of mortality of control and PVC/Administered rats, no details are given of population sizes, pattern and causes of death or histopathology other than of lung tissue.

Malignant Tumours of the Liver and Lungs in an Area with a PVC Industry. Šarić, M. et al (1976). Environmental Health Perspectives, 17, 189-192

"The incidence of malignant tumors of the lung and bronchus and of cytologically confirmed primary malignant tumor of the liver was analyzed for a 4-year period in a city with several factories, including a PVC industry. Prior to the study of two cases of angiosarcoma of the liver were diagnosed in workers employed in PVC production.

The total incidence of analyzed tumors was only slightly higher than predicted. The tumors of the liver recorded did not show any dependence on place of work or residence. During the period of observation, malignant tumors of the bronchus (lung) were not recorded in the PVC industry. Their rate in the area in which the PVC industry is situated was approximately the same as that for the entire city area.

The study does not indicate that the occurrence of malignant tumors other than angiosarcoma is associated with exposure to vinyl chloride."

The period of observation was too short for a definitive conclusion to be reached: furthermore, a substantial proportion of persons with lung cancer could not be adequately investigated.

An Epidemiological Investigation of an Excess Lung Cancer Risk in a Synthetic Chemical Plant. Waxweiller, R.J. et al (1978) NIOSH

While this does not conclusively demonstrate a causal relationship between exposure to PVC dust and lung cancer, it indicates such a possibility and merits further consideration.

Works of Wagner, J.C.

In a series of personal communications, he has reported the presence of PVC particles in lung sections obtained from PVC workers. In his animal studies, intra-pleural instillation has shown there to be dissemination with evidence of particles present in lung sections. His inhalation study on rats showed there to be pulmonary fibrosis and multiple granulomas.

Pathology of Polyvinyl Resins. Broussard, G. (1969) Folia Medica 52, 102-108

This paper claims that PVC resin powder on inhalation accumulates in the lung with a consequent loss of alveolar surface. He considers the powder insoluble and inactive. He further considers that when mixed powders are inhaled pulmonary fibrosis may develop with a restricted ventilation defect, alteration in the alveolar-capillary permeability, and an obstructive or combined type of defect in the case of pulmonary fibrosis. The radiological appearance is said to be reticulation with enlargement of the hilar lymph nodes or a micronodular appearance without enlargement of the hilar lymph nodes. Clinically, chronic bronchitis with progressive respiratory insufficiency, alternating with periods of remission of the symptoms are said to occur.

Unfortunately there are no hard data to support these contentions and although several references are listed at the end of the paper it is uncertain as to what support they give to the asseverations of this paper.

Radiological and Lung Function Studies of Workers Exposed to Polyvinyl Chloride Dust. Burrows, G.E. et al (1978?) Personal Communication Summary

" The results of a number of studies on the effects of PVC dust both in vitro and

in animals and man have been conflicting. The present studies performed in 1976 and 1977 consist of chest radiological and lung function assessment of male workers exposed to PVC dust. In 1976 Chest X-rays were taken on 179 men exposed and 63 men not exposed to PVC dust. In 1977 209 men; 104 exposed to PVC dust only, 112 exposed to solvents only and 294 exposed to a mixture of both, agreed to fill in the MRC questionnaire on respiratory function and performed simple spirometric tests.

The radiological survey showed no pneumoconiosis and the proportion of all abnormalities was the same in the two groups.

Lung function, forced expiratory volume ($FEV_{1.0}$) and forced vital capacity (FVC) were determined for members of each of the three groups. No differences were found after allowance was made for age, height and smoking.

When service and smoking effects were separately considered, the latter is shown to be the dominant cause of reduced function.

Work with PVC dust has not produced deleterious effects on lung function in this study."

There are a number of observations one might make on this study. Thus it would be helpful to know more about the background to the x-ray study in terms of response rate, turnover of employees etc., Although the MRC questionnaire was employed, (the method of administration was not a standard one) the results are not discussed. The pulmonary function study reveals large standard deviations suggesting that the study was not adequate for detecting moderate differences in lung function between the exposure groups even if these had been present. If pneumoconiosis under the circumstances of this particular study had a low prevalence, it would be easily be missed in a study of this nature. Ideally, one would have wanted a total population study with standardised methods of observation (x-ray reading, symptomatic enquiry and lung function) and analyses admitting the most heavily exposed to be studied separately. This paper does not resolve the position vis-à-vis the respiratory effects of PVC inhalation.

Various Studies of Meat Workers Asthma

While these relate to emissions from heated labels and wrapping material, there is evidence in some cases, that disease may be due to components such as phthalic anhydride, 2, 5 - di-tert-amyl quinone and dicyclohexylphthalate. Other irritant substances may also be formed. While these reports have no immediate bearing, they underline the importance of considering the composition of compounded resin

*NIOSH Animal Studies - Reports dated 14th May 1977 (Rats), 20th May 1977 (Guinea Pigs) and 6th September 1977 (Monkeys) - and Current Comments

This was a 12 month study only of rats exposed to PVC at 10 mg/m³ for 6 hours/day for 5 days/week. 5 exposed rats and 64 control male rats were used. It was concluded that there was no inflammatory or other deleterious effects seen in the lung of exposed animals that could be attributable to PVC inhalation.

Male guinea pigs were similarly exposed for a 12 month period (36 exposed, control 30). As with the rats there were more macrophages present in the lungs of exposed animals but it was concluded that no inflammatory or other deleterious effects seen in the lungs of these animals could be attributable to PVC inhalation.

10 male Cynomolgus monkeys were exposed to similar levels for almost 22 months. It was concluded that the only contribution of the inhaled PVC dust deposition and retention to pulmonary tissue morphology, was numerous aggregations of PVC-containing macrophages.

The report of plant material in the lungs of exposed animals could have affected interpretation in certain circumstances. It is difficult to reconcile the results of these experiments with others reported. The studies were not set up to determine carcinogenic properties of PVC dust, which incidentally is not specified in the documents available. In a letter to the Chief of the Pathology section at NIOSH, B.F.Goodrich Chemical Company, both Geon 121 and Geon 92 are referred to. Which was used in these studies was not specified in the papers available.

PVC Chronic Inhalation Toxicology Study

A document which is a photocopy of two pages of typescript and one table with no attribution is present on the department files. The clue to its origin lies in the following quotation:

> "In light of the relationship unequivocally established between occupational exposure to vinyl chloride monomer and liver angio-sarcoma and the concern expressed on potential risk to human health from exposure to polyvinyl chloride (PVC) dust manufactured and used from polymerization of the vinyl chloride monomer, OSHA in FY'75 initiated project plan on "Chronic Exploratory Toxicology Studies and Tests of Validity of Industrial Air Standards" proposed an inhalation exposure study with PVC dust. Actual exposures to a representative material (B.F. Goodrich Company (Geon 121) began in February 1976 utilising 3 species of animals - monkey, guinea pig and rat....."

Although there are certain numerical discrepancies between this apparent summary paper and the Zapata study report [illegible] by NIOSH, it is possible that they refer to the same study. Nevertheless the abstract refers to further data not included in the NIOSH reports including pulmonary function of the monkeys and biochemical/clinical chemistry on [illegible] pig and rat. Tests for liver damage were relatively insensitive so that it is not possible to conclude that there was no liver damage but only that no extensive functional liver damage occurred. The monkey pulmonary function tests suggest [illegible] loss of lung recoil pressure probably as the result of ageing and there was some indication of small air-way obstruction of non-statistical significance. At [illegible] compared with pre-exposure data of lung function no significant differences were observed.

Functional Respiratory Changes upon Chronic Exposure to Monomeric and Polymeric Vinylchloride. Mapp, C (1978) Istituto Medicina del Lavoro, 69, 151-162

258 workers producing polyvinyl chloride were studied by respiratory symptom questionnaire, lung function radiography etc. In their conclusions the authors consider that vinylchloride monomer has adverse effect on lung function which is generally moderate in terms of prevalence and severity as distinct from a foreign body type reaction due to polymer. They raise the possibility of a potentiation of effects between monomers, polymer powders and tobacco which can lead to obstructive disease and symptoms of chronic bronchitis.

CONCLUSIONS

The additional studies reviewed do not disprove the suggestion that the long term inhalation of PVC dust ('pure' and compounded) may be a hazard to man in terms of respiratory disease (malignant and non-malignant) or disease of other systems.

M GREENBERG
JANUARY 1979