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Exposure to vinyl chloride monomer: report on a cohort study

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ABSTRACT In 1980 a prospective exposed/non-exposed cohort study was initiated in France by the Institut National de la Santé et de la Recherche Médicale (INSERM U 287) to evaluate the association between mortality and cancer morbidity and occupational exposure to vinyl chloride monomer (VCM). Eleven hundred VCM exposed subjects and 1100 VCM non-exposed controls matched for age (±2 years), plant, and physician were included and followed up over a five year period for vital, health, and occupational status. The percentages of deaths observed among the exposed (1·8%) and non-exposed subjects (1·6%) did not differ. Eighteen (1·6%) and 15 (1·4%) cases of cancer were reported among exposed and non-exposed subjects, respectively (NS). One case of angiosarcoma of the liver occurred among the exposed group; six cases of lung cancer occurred among exposed subjects and two among non-exposed subjects (NS). The percentage of diseases of the circulatory system was higher ($p < 0·02$) in the exposed group than in the non-exposed group: this difference was explained mainly by the high incidence of Raynaud's disease ($p < 0·006$). The percentages of diseases of the respiratory system did not differ between the two groups.

Several epidemiological studies of subjects occupationally exposed to vinyl chloride monomer (VCM) have been conducted.[1–19] Although these studies differ in size and design, and cover different periods, they all conclude that the risk of some diseases, angiosarcoma of the liver (ASL) and acrosteolysis, for example, is increased by exposure to VCM. In 1980 a prospective exposed/non-exposed cohort study was initiated by the Institut National de la Santé et de la Recherche Médicale (INSERM U 287) in France. The main purpose of this study was to evaluate the association between mortality and morbidity (especially from malignant tumours) and occupational exposure to VCM.

Materials and methods

The present study included most of the French VCM polymerisation plants. The exposed group consisted of 40–55 year old employees, either presently exposed or having been exposed to VCM. Foreigners were included if they had been living in France with their family for at least five years. Controls were employees never exposed to VCM. Each control was matched to one exposed subject for age (±2 years), plant, and physician. Interviews for initial data collection were conducted by each plant physician over a year. Data collected included identification, employment history (the entire work history was coded), occupational category, and amount of exposure to VCM (defined for polymerisation functions as low since 1976, moderate between 1970 and 1976, and high before 1970), and medical history in addition to smoking and drinking habits. Each year until December 1985 the subjects were followed up for vital, health, and occupational status. Causes of death and specific abnormalities were coded according to the International Classification of Diseases (ICD, 9th revision). Subjects who had terminated their employment (resigned, transferred, or retired) were followed up by each physician by post.

The data were analysed using the PIGAS system.[20] Control for confounding factors, such as cigarette smoking, alcohol consumption, and socioeconomic status, was performed using the Mantel-Haenszel procedure.[21]

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Table 1 *Distribution of subjects by plant*

	No of subjects (%)
Tavaux (Solvay)	886 (40)
Saint-Fons (Atochem)	656 (30)
Roussillon (Rhone-Poulenc)	170 (8)
Aubervilliers (Rhone-Poulenc)	124 (6)
Lavera (Atochem)	110 (5)
Saint-Auban (Atochem)	84 (4)
Bully-les-Mines (CDF Chimie)	70 (3)
Ribecourt (Rhone-Poulenc)	30 (1)
Port-de-Bouc (Atochem)	22 (1)
Commentry (AEC Rhone-Poulenc)	18 (1)
Montluel (Atochem)	18 (1)
Antony (Rhone-Poulenc)	12 (1)
Total	2200

Results

From June 1980 to May 1981, 2200 employees were included: 1100 exposed and 1100 controls in 12 plants (table 1). Two plants recorded over 70% of the entire cohort.

DESCRIPTION OF THE CHARACTERISTICS OF THE COHORT

Most initial characteristics, smoking, and drinking habits did not differ among exposed and non-exposed subjects (table 2).

A socioeconomic characteristic was defined. Employees whose occupational activity was coded as worker for more than 75% of their entire work history were considered as blue collar workers; the remainder were classified as white collar workers. These percentages did not differ between the two groups.

DESCRIPTION OF EXPOSURE TO VCM

At the time of the interview, only 36% of the exposed group was exposed to VCM, the rest having been exposed in the past. They represented the following occupations: CV synthesis (17%), polymerisation (54%), copolymerisation (7%), and compoundage and pharmacy (22%). The mean (±SD) total duration of exposure to VCM was 14 years (±8) and the mean time between the first exposure and interview was 18 years (±8). The amount of exposure having been coded as low, moderate, or high, there were seven different combinations of exposure level during the entire work history of exposed employees. Table 3 shows the distribution of exposed subjects according to these combinations, the mean exposure duration at each level, and the time between the first exposure and the interview.

FOLLOW UP OF THE COHORT

The follow up of the two groups was similar. By 1985, 15% of the subjects initially included had retired, 2% had resigned or been transferred, and 4% were on sick leave. The percentage of subjects lost to follow up

Table 2 *Initial characteristics of exposed and control groups*

	Exposed (n = 1100)	*Controls (n = 1100)*	*p*
Age (mean ± SD, years)	47 ± 4	48 ± 4	NS
Foreigners	14%	14%	NS
Urban residence*	46%	45%	NS
Smoking habits:			
Non-smokers	27%	24%	
Smokers	42%	46%	NS
Ex-smokers	31%	30%	
Duration since stopping smoking (mean ± SD, years)	8 ± 7	8 ± 7	NS
Daily consumption (mean ± SD):			
Cigarettes	16 ± 8	16 ± 9	NS
Pipes	5 ± 5	5 ± 6	NS
Cigars	4 ± 4	4 ± 4	NS
Duration smoking (mean ± SD, years):			
Cigarettes	23 ± 8	24 ± 8	NS
Pipes	16 ± 10	18 ± 11	NS
Cigars	8 ± 8	9 ± 9	NS
Inhalation	62%	64%	NS
Drinking habits:			
Non drinkers†	13%	12%	NS
Weekly consumption (mean ± SD)‡	32 ± 23	31 ± 20	NS
Clinical signs of alcoholism	15%	11%	0·003
Socioeconomic status:			
Blue collar workers§	75%	72%	NS

*City of 15 000 inhabitants or more.
†Subjects not drinking wine, beer, fortified wines, or hard liquors.
‡Sum of glasses of wine, beer, fortified wines, and hard liquors.
§Workers for more than 75% of their entire work history.

Table 3 *Distribution of exposed subjects according to levels of exposure to VCM*

*Level**	%	*Duration of exposure* mean ± SD (years)*	*Time between 1st exposure and interview mean ± (years)*
1	37	D = D1 = 11 ± 7	14 ± 8
2	13	D = D2 = 9 ± 8	17 ± 7
3	8	D = D3 = 9 ± 7	18 ± 8
1 + 2	14	D = 16 ± 7	
		D1 = 8 ± 5	19 ± 6
		D2 = 8 ± 6	
1 + 3	10	D = 18 ± 8	
		D1 = 10 ± 7	22 ± 7
		D3 = 8 ± 6	
2 + 3	3	D = 20 ± 9	
		D2 = 11 ± 7	24 ± 7
		D3 = 9 ± 6	
1 + 2 + 3	16	D = 21 ± 4	
		D1 = 7 ± 3	22 ± 5
		D2 = 7 ± 4	
		D3 = 6 ± 5	

*1 = Low, 2 = moderate, 3 = high.
†D = Total exposure duration, D1 = level 1 exposure duration; D2 = level 2 exposure duration, D3 = level 3 exposure duration

during the five years—that is, whose vital and health status was unknown—was 3%. These percentages did not differ between exposed and non-exposed groups (table 4).

MORTALITY OF THE COHORT

During the five year follow up period, 20 (1·8%) exposed and 17 (1·6%) non-exposed subjects died. These percentages did not differ significantly. Table 5 shows the causes of death.

MORBIDITY OF THE COHORT

During the five year follow up period, 18 (1·6%) and 15 (1·4%) cases of cancer were reported among exposed and non-exposed subjects, respectively. These percentages did not differ significantly. The distribution of cancer sites is presented in table 6. One case of angiosarcoma of the liver occurred among the exposed group. Eight cases of lung cancer were reported, six among the exposed subjects (0·5%) and only two among the non-exposed subjects (0·2%); the percentages of lung cancer did not differ between the two groups. The percentage of diseases of the circulatory system (ICD: 390–459) was higher ($p < 0·02$) among the exposed group (10%) than among the control group (7%) (table 7). Six categories were considered: hypertension, coronary insufficiency, cerebrovascular disease, arteriosclerosis of the limbs, Raynaud's disease, and other vascular diseases The only association found concerned Raynaud's disease, and other vascular diseases. The only association found concerned Raynaud's disease ($p < 0·007$).

The percentage of diseases of the respiratory system (ICD: 460–519) did not differ between the two groups and no case of pulmonary fibrosis was recorded. These results were not materially altered by adjustment for tobacco smoking, alcohol status, and socioeconomic category.

Discussion

Subjects were included in the study if they were under 55 in order to allow a five year minimal follow up without too many withdrawals, as retirement usually takes place around age 55–60. Moreover, the subjects had to be over 40 for two reasons: firstly, to include only subjects who had been exposed to VCM for a sufficiently long time when levels of exposure were appreciably higher than at present and, secondly, because the incidence of malignant disease increases with age.

Considering the percentage of retired, resigned, or transferred subjects, the percentage of subjects lost to follow up (3%) is low. This results from each physician's personal acquaintance with the employees under his care In this type of occupational study the

Table 4 *Distribution of subjects according to follow up status*

	Lost to follow up	*Resigned or transferred*	*On sick leave*	*Retired*
Exposed (1100)	24(2%)	27(3%)	44(4%)	155(14%)
Controls (1100)	39(4%)	25(2%)	33(3%)	163(15%)
p	NS	NS	NS	NS

Table 5 *Causes of death observed during five year follow up period**

	Exposed (1100)	Controls (1100)
All causes	20	17
Cancer	9	11
Circulatory system	5	3
Cirrhosis	0	2
Trauma	3	1
Others	3	0

*No differences were statistically significant

exposed group is exposed not only to VCM but also to various other agents with possible pathological effects. To control for these different exposures, the control group included workers whose exposure was similar to that of the exposed subjects, except for VCM. Exposed and non-exposed subjects were not matched by socioeconomic characteristics but the percentage of blue collar workers did not differ between the two groups; moreover an adjustment for this factor was made.

The mean time between the first exposure to VCM and the interview was 18 years. This is important, because a long gap is necessary between exposure and the onset of disease, especially in the case of cancer, which may take eight to ten years to develop.

Most surveys have shown a significant reduction in the mortality of VCM workers as compared with mortality in the general population; this is called the "healthy worker effect."[1 7 11 14 15] This study, however, as well as other epidemiological studies comparing exposed and non-exposed workers,[4 5 8] found no difference in mortality between the two groups.

Most studies clearly conclude that the target organs for VCM include the liver, the brain, the lung, and probably the lymphohaematopoietic system, the buccal cavity, and the skin (malignant melanoma). Our results are not consistent with those previously reported. In our study no significant association between cancer morbidity and exposure to VCM was observed, and tumours at the following sites were recorded: angiosarcoma of the liver (one exposed), skin (one exposed, one control, both epitheliomas), buccal cavity (one exposed, three controls), lymphohaematopoietic system (one exposed), and lung (six exposed, two controls). Although the number of cases of lung cancer was three times greater in the exposed than in the non-exposed group, the difference was not significant.

Table 6 *Causes of cancer observed during five year follow up period* (ICD No 140–209)*

	Exposed (1100)	Controls (1100)
All cancers.	18	15
Lung	6	2
Digestive organs	5	6
Skin	1	1
Buccal cavity-pharynx	1	3
Angiosarcoma of liver	1	0
Pancreas	0	1
Lymphohaematopoietic	1	0
Bone	1	0
Kidney	1	0
Unknown	1	2

*No differences were statistically signficant

Table 7 *Percentages of circulatory and non-neoplastic respiratory diseases observed during five year follow up period*

	Exposed (1100)	Controls (1100)	p
Respiratory system (460–519)	3%	2%	NS
Circulatory system (390–459)	10%	7%	0·02
Hypertension (401–405)	4%	3%	NS
Coronary insufficiency (410–414)	2%	2%	NS
Cerebral vascular disease (430–438)	1%	0%	NS
Arteriosclerosis of limbs (4476, 4479, 4402)	1%	1%	NS
Raynaud's disease (4430)	1%	0%	0·007
Other circulatory disorders	2%	2%	NS

In our study a higher percentage of diseases of the circulatory system was observed among the exposed group compared with the controls. This result is consistent with others.[1 4 7 11] The difference was explained mainly by the high incidence of Raynaud's disease but also by the addition of small differences observed in most of the vascular categories considered, whose physiopathology may be the same as for Raynaud's disease. A possible relation between exposure to VCM and the occurrence of hypertension or coronary insufficiency has been reported.[12 18]

Although suggested by some authors,[3 16] we found no association between exposure to VCM and respiratory disease.

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References

1 Tabershaw IR, Gaffey WR. Mortality study of workers in the manufacture of vinyl chloride and its polymers. *J Occup Med* 1974;**16**:509–18

2 Lilis R, Anderson HA, Nicholson WJ, Daum S, Fischbein AS, Selikoff IJ. Prevalence of disease among vinyl chloride and polyvinyl chloride workers. *Ann NY Acad Sci* 1975;**246**:22–41

3 Miller A, Teirstein AS, Chuang M, Selikoff IJ. Changes in pulmonary function in workers exposed to vinyl chloride and polyvinyl chloride. *Ann NY Acad Sci* 1975;**246**:42–52.

4 Nicholson WJ, Cuyler Hammond E, Seidman H, Selikoff IJ. Mortality experience of a cohort of vinyl chloride polyvinyl chloride workers. *Ann NY Acad Sci* 1976;**246**:225–30

5 Ott MG, Langner RR, Holder BB. Vinyl chloride exposure in a controlled industrial environment: a long-term mortality experience in 594 employees. *Arch Environ Health* 1975;**30**:333–9

6 Wyatt RH, Kotchen JM, Hochstrasser DL, *et al.* An epidemiologic study of blood screening tests and illness histories among chemical workers involved in the manufacture of polyvinyl chloride. *Ann NY Acad Sci* 1975;**246**:80–7

7 Fox AJ, Collier PF. Low mortality rates in industrial cohort studies due to selection for work and survival in the industry. *Br J Prev Soc Med* 1976;**30**:225–30.

8 Waxweiler RJ, Stringer W, Wagoner JK, Jones J. Neoplastic risk among workers exposed to vinyl chloride. *Ann NY Acad Sci* 1976;**271**:40–8.

9 Brady J, Liberatore F, Harper P, *et al.* Angiosarcoma of the liver: an epidemiologic survey. *JNCI* 1977;**59**:1383–5

10 Chiazze L, Nichols WE, Wong D. Mortality among employees of PVC fabricators. *J Occup Med* 1977;**19**:623–8

11 Fox AJ, Collier PF. Mortality experience of workers exposed to vinyl chloride monomer in the manufacture of polyvinyl chloride in Great Britain. *Br J Ind Med* 1977;**34**:1–10

12 Waxweiler RJ, Falk H, McMichael A, Mallov JS, Scott Grivas A, Stringer WT. *A cross-sectional epidemiological survey of vinyl chloride workers.* Cincinnati: Department of Health, Education, and Welfare, 1977 (NIOSH publ No 77–177.)

13 Anderson HA, Snyder J, Lewinson T, Wood C, Lilis R, Selikoff IJ. Levels of CEA among vinyl chloride and polyvinyl chloride exposed workers. *Cancer* 1978;**42**:1560–7.

14 Equitable Environmental Health, Inc. *Epidemiological study of vinyl chloride workers.* (Final report submitted to Manufacturing Chemists Association.) Washington: EEH, 1978

15 Pierre C, Tassignon JP. Etude de la mortalité chez des travailleurs exposés au chlorure de vinyle. *Archives des Maladies Professionnelles, de Medecine du Travail et de Sécurité Sociale* 1979;**40**:1131–45.

16 Theriault G, Allard P. Cancer mortality of a group of Canadian workers exposed to vinyl chloride monomer. *J Occup Med* 1981;**23**:671–6

17 Forman D, Bennett B, Stafford J, Doll R. Exposure to vinyl chloride and angiosarcoma of the liver: a report of register of cases. *Br J Ind Med* 1985;**42**:750–3

18 Greiser E, Reinl W, Weber H. Vinylchlorid-exposition und mortalitat Deutscher chemiearbeiter im vergleich zur mortalitat nichtexponierter chemiearbeiter und PVC-verarbeiter. *Prophylaxe und Ergonomie* 1982;**32**:44–62.

19 Storetvedt Heldaas S, Langard SL, Andersen A. Incidence of cancer among vinyl chloride and polyvinyl chloride workers. *Br J Ind Med* 1984;**41**:25–30

20 Wartelle M, Kramar A, Jan P, *et al.* PIGAS, an interactive statistical data base management system. In: *Proceedings of the second international workshop on statistical database management.* Los Altos: Laurence Berkely Laboratory, Statistics Canada, 1983.124–32

21 Mantel N. Chi-square tests with one degree of freedom: extension of the Mantel-Haenszel procedure. *Journal of the American Statistical Association* 1963;**58**:690–700

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Correspondence

Update on lung disease in coal miners

SIR—In his editorial (1987;**44**:145–8) Soutar fortifies some of his arguments by quoting two papers that describe certain investigations carried out by my colleagues and me when I was associated with the National Institute of Occupational Safety and Health. In doing so, he either quotes out of context or misinterprets several of our findings.

Firstly, in his remarks concerning coalworkers' pneumoconiosis, he states that "irregular opacities are related to dust exposure ... and to an impairment of lung function." He supports this comment by quoting, among other references, a paper by Amandus *et al.*[1] In reality, Amandus and his coworkers found that the two main factors associated with the presence of irregular opacities in coalminers were cigarette smoking and increasing age. A surrogate measure of exposure to dust—namely, years worked underground—was also associated to a far lesser degree. Moreover, in non-smoking coal miners irregular opacities were not associated with impaired lung function. In virtually every investigation of the frequency and presence of irregular opacities, whether in coalminers or other dust exposed populations, there has been an association between prevalence of irregular opacities and cigarette smoking. It is abundantly apparent that irregular opacities are found in many occupations other than coalmining, including workers exposed to kaolin,[2] man made mineral fibres,[3] and silica.[4] In addition, they have been noted to occur in non-dust exposed groups including women and here again, cigarette smoking played a pre-eminent part.[5,6] Certainly, one cannot attribute the presence of irregular opacities in non-smoking granite shed or man made mineral fibre workers to emphysema and fibrosis. No one has yet suggested that exposure to silica in the absence of conglomerate silicosis leads to emphysema.[7] Surely coalminers are susceptible to the same influences and agents that lead to the presence of irregular opacities in other dust and non-dust exposed workers. The power and validity of the association between coaldust and irregular opacities are relatively weak and multiple regression analysis becomes less reliable when there is collinearity between such factors as age, cigarette smoking, and exposure to dust. The association between them becomes even more tenuous when the interobserver variation in regard to the reading of irregular opacities is taken into consideration.[8] Although the paper quoted to indicate the problem with wide interobserver variation originates from the United States, I have similar unpublished data from Britain.

Secondly, Soutar postulates that there is "an element of restrictive lung defect in coalminers" since, in the dust exposed groups, both the FEV_1 and FVC are reduced. Contrary to what he states, obstruction is often associated with a decrease in both the FEV_1 and FVC, but by contrast, the residual volume (RV) is always increased and the total lung capacity (TLC) is often increased.[9,10] In true restrictive impairment, all lung volumes are decreased. An increased RV is an early sign of obstructive impairment and the increase occurs at the expense of the FVC.[9–11] Later, the TLC also increases but to a lesser extent; when it does so it partially and temporarily masks the effects of the increase in the RV. In the absence of a knowledge of all lung volumes the mere presence of a reduction in the FEV_1 and FVC cannot be taken as an indication that restrictive impairment is present. If Soutar rereads our paper he will note that one of the points we made was that the RV was appreciably increased in smokers whether they had bronchitis or not.[12] There was, in addition, a slight but significantly increased RV in non-smokers who had industrial bronchitis or what he terms occupational bronchitis (fig 4). Secondly, he will note that we did not suggest that the airflow limitation occurs in the upper airways, although we believe that most of the obstruction is located in central airways. Indeed our exact words were "flows at low lung volumes were unchanged unless expressed either at absolute lung volumes or as a percentage of TLC, this being a reflection of an increase in RV." Finally, although he maintains that some coalminers showed severe airflow obstruction due to dust exposure, he concedes that most are smokers and yet attributes the airflow obstruction mainly to dust exposure. This statement is difficult to reconcile with the postmortem study carried out by Fernie *et al* at the institute in which they were unable to find evidence of pulmonary hypertension or cor pulmonale in the absence of a history of cigarette smoking or PMF.[13]

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References

1 Amandus HE, Lapp NL, Jacobsen G, Reger RB. Significance of irregular small opacities in radiographs of coalminers in the USA. *Br J Ind Med* 1976;**33**:13–7.
2 Wagner JC, Pooley FD, Gibbs A, *et al*. Inhalation of china stone and china clay dusts: relationship between mineralogy of dust retained in the lungs and pathological changes. *Thorax* 1986;**41**:190–6.
3 Weill H, Hughes JM, Hammad YY, *et al*. Respiratory health in workers exposed to man-made mineral fibers. *Am Rev Respir Dis* 1983;**128**:104–12.

4 Theriault GP, Peters JM, Johnson WM. Pulmonary function and roentgenographic changes in granite dust exposure. *Arch Environ Health* 1974;**28**:23–7.
5 Carilli AD, Kotzen LM, Fischer MJ. The chest roentgenogram in smoking females. *Am Rev Respir Dis* 1973;**107**:133–6.
6 Weiss W. Cigarette smoking, asbestos and small irregular opacities. *Am Rev Respir Dis* 1984;**130**:293–301.
7 Sussman NB, Townsend MC, Mazumdar S. Effects of multicollinearity on inference in regression analysis of occupational respiratory epidemiologic data. *Am Rev Respir Dis* 1986;(suppl) A156.
8 Amandus HE, Pendergrass EP, Dennis JM, Morgan WKC. Pneumoconiosis: interreader variability in the classification of the type of small opacities in the chest roentgenogram. *Am J Roent Rad Therapy Nuc Med* 1974;**122**:740–3.
9 Levine G, Housley E, MacLeod P, Macklem PT. Gas exchange abnormalities in mild bronchitis and asymptomatic asthma. *N Engl J Med* 1970;**282**:1277–80.
10 Meisner P, Hugh-Jones P. Pulmonary function in bronchial asthma. *Br Med J* 1968;**1**:470–2.
11 Thurlbeck WM, Henderson JA, Fraser RG, Bates DV. Chronic obstructive lung disease. *Medicine* 1970;**49**:81–145.
12 Hankinson JL, Reger RB, Morgan WKC. Maximal expiratory flows in coalminers. *Am Rev Respir Dis* 1977;**116**:175–80.
13 Fernie JM, Douglas AN, Lamb D, Ruckley VA. Right ventricular hypertrophy in a group of coalminers. *Thorax* 1983;**38**:436–42.

Dr Soutar replies:

Morgan takes issue with some of my necessarily brief remarks on small irregular opacities in the chest radiographs of coalminers, and the type of lung functional impairment related to exposure to coalmine dust.

It is not disputed that irregular opacities in coalminers are related to age and may be related to smoking. I quoted evidence that irregular opacities are related also to a surrogate index of dust exposure (years worked underground)[1 2] and to direct measurements of cumulative exposures to dust.[3] Despite his doubts, Morgan associates himself with the paper by Amandus *et al*,[1] in which the authors state "smoking, age, and years underground were independent factors which each contributed significantly to the prevalence of irregular lesions."

Inter-reader differences in the interpretation of the appearances of the chest radiographs are well recognised,[3 4] but agreement between readers may still be sufficient under some circumstances to enable the demonstration of relations between certain radiographic appearances and other variables. Amandus *et al* (Morgan among the authors) studied inter-reader differences in recognising irregular opacities, and recommended that "epidemiological studies that depend on the differentiation of these types of opacity should involve a majority opinion from several interpreters rather than relying on one reader only. In addition the rigid training of readers periodically by the same standards should help to keep this variation within acceptable limits."[4] Observing these precautions Dick *et al* confirmed a positive relation between irregular opacities and lifetime cumulative dust exposure which is unlikely to be due to chance.[3]

Referring to the functional implications of irregular opacities, Morgan correctly states that Amandus *et al* showed impairment of function related to irregular opacities in smokers but not in non-smokers.[1] In addition to the other evidence I quoted of functional impairment related to irregular opacities,[1 5 6] a new study confirms impairments of function related to irregular opacities in coalminers.[7] Most (86%) of the coalminers were smokers or ex-smokers, but results from 104 non-smokers included in that study were consistent with an opacity related impairment in these men also.

Secondly, (Morgan's notation), of course restrictive functional defects cannot be identified with complete confidence on the basis of spirometric measurements alone, though some patterns of abnormality can be suggestive. Our epidemiological studies have shown that dust exposure is related on average to a parallel reduction of FEV_1 than FVC, a pattern contrasting with the effects of smoking, which is related to a much greater reduction of FEV_1 than FVC, and corresponding reduction of the FEV_1/FVC ratio.[8] The former pattern is also shown by the group of non-smoking miners with bronchitis (assumed to be "industrial bronchitis") described by Hankinson *et al*.[9] Table 1 in their paper shows that FEV_1, FVC, and FEV_1/FVC ratio in these men were on average 0·17 l, 0·18 l, and 0·3% respectively lower than in an age and height matched group of non-smoking miners without bronchitis. By contrast, the FEV_1, FVC, and FEV_1/FVC ratio in a group of smoking miners with bronchitis were 0·43 l, 0·23 l, and 5·5% respectively lower than in the non-smoking miners without bronchitis. Trying to understand these differences in conventional terms, I suggested in relation to dust induced defects "an element of a restrictive lung defect as well as airflow obstruction." Morgan for his part suggested on the basis of these and additional measurements "that dust induced bronchitis is primarily affecting the larger or upper airways, and is not associated with concomitant destruction of lung parenchyma" (page 178, 3rd para, lines 14–17), while later in the article suggesting additional changes in small airways.[9]

To resolve these differences, further characterisation of the functional effects of dust exposure is needed, and this will be available shortly. This new information may enable the disabling pathological lesions eventually to be identified by helping to direct the pathologist's attention to the relevant parts of the lung.

Finally Morgan refers to my mention of a small group of coalminers who showed a severe inverse relation between dust exposure and FEV_1. Our reasons

for attributing the decrement in FEV_1 to exposure to dust are explained clearly in the source paper[10]; and just as we are not yet clear on the functionally important pathological changes related to dust, we also have little basis on which to judge the relevance of Morgan's point on pulmonary hypertension or cor pulmonale. Incidentally, the study by Fernie *et al* included only eight non-smoking miners without progressive massive fibrosis,[11] too small a group to provide substantial support for Morgan's argument.

References

1 Amandus HE, Lapp NL, Jacobson G, Reger RB Significance of irregular small opacities in radiographs of coalminers in the USA. *Br J Ind Med* 1976;**33** 13–7.

2 Cockcroft A, Lyons JP, Anderson N, Saunders MJA Prevalence and relation to underground exposure of radiological irregular opacities in south Wales coal workers with pneumoconiosis. *Br J Ind Med* 1983;**40**:169–72

3 Dick JA, Jacobsen M, Gauld S, Pern PO The significance of irregular opacities in the chest radiographs of British coal miners. In: *Proceedings of the VI International Pneumoconiosis Conference, Bochum, 1983*. Geneva International Labour Office, 1984:283–99

4 Amandus HE, Pendergrass EP, Dennis JM, Morgan WKC. Pneumoconiosis: inter-reader variability in the classification of the type of small opacities in the chest roentgenogram *Am J Roent Rad Therapy Nuc Med* 1974,**122**:740–3

5 Cockcroft A, Berry G, Cotes JE, Lyons JP Shape of small opacities and lung function in coal-workers. *Thorax* 1982,**37**:765–9

6 Musk AW, Cotes JE, Bevan C, Campbell MJ Relationship between types of simple coalworkers' pneumoconiosis and lung function. A nine year follow-up study of subjects with small rounded opacities. *Br J Ind Med* 1981;**38**.313–20.

7 Collins HPR, Dick JA, Bennett JG, *et al*. Irregularly shaped small shadows on chest radiographs, dust exposure, and lung function in coalworkers' pneumoconiosis. *Br J Ind Med* (in press).

8 Soutar CA, Hurley JF. Relation between dust exposure and lung function in miners and ex-miners *Br J Ind Med* 1986;**43** 307–20.

9 Hankinson L, Reger RB, Morgan WKC Maximal expiratory flows in coalminers. *Am Rev Respir Dis* 1977,**116**:175–80.

10 Hurley JF, Soutar CA. Can exposure to coalmine dust cause a severe impairment of lung function? *Br J Ind Med* 1986;**43**.150–7.

11 Fernie JM, Douglas AN, Lamb D, Ruckley VA. Right ventricular hypertrophy in a group of coalworkers *Thorax* 1983,**38**.436–42

Incidence of cancer among vinylchloride and polyvinylchloride workers: further evidence for an association with malignant melanoma

SIR—Recently Heldaas *et al* presented the results of a cancer morbidity study in vinylchloride exposed workers (1987;**44**:278–80). They are suggesting a relation between exposure to VC and the incidence of malignant melanomas. This suggestion is based on visual comparison of observed/expected cases in subgroups, stratified on levels of exposure or on years from first exposure (resp tables 1 and 2).

A statistically significant trend between duration or level of exposure and specific cancer morbidity may be tested according to Breslow *et al*. This test on significant trend was applied on the observed/expected cases of melanoma in relation to level of exposure (table 1) or in relation to years from first exposure (table 2). The probability, that the distribution of observed/expected cases of melanoma in the subgroups of table 1 and 2 was due to chance, was respectively 65% and 22%.

The only significant finding is the increase in the number of cases of melanoma in the total group of workers. Such an increase, however, was also found in cohort studies of workers with widely differing occupations. Moreover, in all other cohort studies of workers exposed to vinylchloride no increase of mortality from melanoma was found.[2] Therefore, the present epidemiologic evidence does not support a causative relation between the incidence of melanoma and exposure to occupational vinylchloride.

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References

1 Breslow NE, Lubin JH, Marck P, Langholz B Multiplicative models and cohort analysis. *Journal of the American Statistical Association* 1983;**78** 1–12.

2 Nicholson WJ, Henneberger PK, Seiderman H Occupational hazards in the VC-PVC industry. *Prog Clin Biol Res* 1984,**141**.155–75

Drs Heldaas, Laugård and Andersen reply:

Ten Berge seems to put a great deal of emphasis on the statistical inference of the results in our study.[1] We are less concerned about the statistics; in our view the emphasis should be put more on the design of the study. We think that the quality of epidemiological studies in occupational medicine should be judged primarily by the characterisation of the level and duration of exposure to the potentially harmful agent, and to what extent selection has been avoided, and whether confounding has been dealt with in a proper way. Occupational diseases with presumed long latency periods have also to be dealt with in a manner which takes care of this phenomenon.

A small sample size is a common weakness in the design phase of small studies. Ten Berge, however, seems to interpret this problem of small sample size and failure to obtain "statistical significance" as being evidence for non-causality. It is not obvious from ten Berge's letter how he has tested statistical significance.

He has, however, avoided discussing the six cases of melanoma versus one expected, which we consider to be the most important result. As pointed out in the previous study[2] studies of cancer incidence have advantages compared with studies of mortality, particularly for tumour sites that are successfully cured.

We feel confident that the methodological aspects have been properly considered in our study.[1] Consequently, we are less concerned as to whether the results are "statistically significant" or not. We consider the fact that two cases of melanoma developed in the a priori high risk group selected from the same VCM exposed population before the performance of the previous study[2] as being of more significance for the interpretation of possible causality than the presence of statistical significance. Development of new cases in a preselected risk group may be of greater significance in a causality discussion than is the presence of "statistically significant" results. As opposed to "statistical significance," a previously selected a priori high risk group cannot be manipulated.

A recent study from Du Pont, USA,[3] seems to support our finding, but apparently our results have not attracted the author's attention.[1 2]

The current lack of adequate animal and in vitro models for studying the development of malignant melanomas makes the study of the possible causal relation between VCM exposure and this tumour complicated. Even so, Maltoni *et al* succeeded in producing malignant melanomas of the skin in Syrian golden hamsters exposed to a wide range of VCM levels,[4] and they concluded that the tumours were related to the exposure.

References

1 Heldaas SS, Andersen A, Langård S. Incidence of cancer among vinyl chloride and polyvinyl chloride workers: a further evidence for an association with malignant melanoma. *Br J Ind Med* 1987;**44**:278–80.

2 Heldaas SS, Langård S, Andersen A. Incidence of cancer among vinyl chloride and polyvinyl chloride workers. *Br J Ind Med* 1984;**41**:25–30.

3 O'Berg MT, Burke CA, Chen JL, Walrath J, Pell S, Gallie CR. Cancer incidence and mortality in the Du Pont Company an update. *J Occup Med* 1987;**29**:245–51.

4 Maltoni C, Lefemine G, Ciliberti A, Cotti G, Carretti D. Carcinogenicity bioassays of vinyl chloride monomer: a model of risk assessment on an experimental basis. *Environ Health Perspect* 1981;**41**:3–29.

Pulmonary fibrosis in asbestos insulation workers with lung cancer

SIR—Rudd's letter (1987;**44**:428–9) points to several interesting questions.

(1) Histopathological pulmonary findings in asbestos insulation workers with long exposure to the dust. I reviewed lung parenchyma sections submitted to me by pathologists in various institutions in the United States and Canada. As expected, the material was taken from various parts of the lung, often unspecified. It is widely accepted that pulmonary asbestosis is characterised microscopically by diffuse interstitial fibrosis caused by inhaled asbestos fibres. This was sought in my examinations in available parenchyma; Rudd argues that the subpleural areas be excluded, a rather arbitrary preference in view of the absence of data that parenchyma here differs from parenchyma elsewhere; particularly since this part of the lung often has a considerable concentration of asbestos fibres, the result of "pleural drift" of inhaled dust. Parenthetically, lung cancer after asbestos inhalation is not infrequently peripheral in origin.

(2) I reported the presence or absence of microscopically evident diffuse interstitial fibrosis. I also reported that in 130 of 138 one or more asbestos bodies were seen. It is commonplace that in single thin (5μ) sections, asbestos bodies may be absent. Does this mean that they are not present (sometimes in large numbers) in the lung? Of course not. The likelihood of showing asbestos bodies varies directly with the amount of tissue studied. They are more readily seen in thick (30μ) sections than thin, more when bulk tissue is digested and filtered than in sections, more when exposure has been to amphiboles than chrysotile, and more when long and thick fibres were inhaled than short and thin. It is thus not enough to say that so many or so many asbestos bodies are seen: one should immediately add comment regarding how much tissue was available for examination and how they were sought. Indeed, in our study, we did not expect to find so many cases (since, occasionally, there was only a single thin section available for review) in which at least one asbestos body was to be seen. My colleagues consider that perhaps this was related to the diligent, prolonged examination to which each slide was subjected.

(3) I was rather surprised to learn from Rudd that in the United Kingdom when there are "too few" asbestos bodies in slides of asbestos workers' lungs the diffuse interstitial fibrosis is not infrequently categorised as cryptogenic fibrosing alveolitis. There must be a great deal of this disease nowadays in the United Kingdom among asbestos workers. And many asbestos workers with diffuse interstitial fibrosis are not eligible for disability compensation.

(4) Asbestos bodies again. I am sure that Rudd is as familiar as we are with the multitude of observations that in lung tissue of asbestos workers with or without lung cancer there tend to be myriads of asbestos fibres uncoated by the iron protein material that allows them to be visible by (relatively insensitive) optical microscopy and thereby seen as asbestos bodies. Generally, the uncoated fibres are demonstrable only by

electron microscopy, after appropriate special preparation of the tissues. It could be—indeed, it is likely—that in the few cases in which we did not observe asbestos bodies, uncoated asbestos fibres would have been seen if we had had an opportunity to examine an adequate tissue sample by electron microscopy. It is perhaps worth noting that we have yet to study an asbestos worker's lung in which we do not find uncoated asbestos fibres (in much larger numbers than in the unexposed general population).

(5) Rudd comments that if our histopathological observations were to be considered evidence of asbestosis in asbestos workers with lung cancer in the United Kingdom many more would be eligible for compensation for lung cancer. Far be it for us to advise how and whether United Kingdom agencies should compensate asbestos workers who suffer lung cancer. We did not proffer such opinions when, until recently, lung cancer was not considered adequate reason for compensation and we will not do it now. Parenthetically, can Rudd tell us what proportion of workers with lung cancer, after important occupational exposure to asbestos, have been denied compensation because a board's histological/asbestos body criteria were not met?

We appreciate Rudd's comments. They reflect important issues in the pathogenesis of lung cancer, not addressed in the bare data reported in our paper but useful as we nowadays grapple with concomitant issues of prevention, compensation, and public health control. Perhaps the letter reflects these: "I do not intend to suggest that the fibrosis seen in these cases was not caused by asbestos exposure." This acknowledgement goes to the heart of the matter. Besides the theoretical pathogenetic connotations, which can be argued about, there are the practical questions of whether and how we might provide help for those found injured after inadequate protection in the past.

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