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July 8, 1987

Ms. Meredith N. Scheck
The Vinyl Institute
Wayne Interchange Plaza #2
155 Route 46 West
Wayne, New Jersey 07470

Re: Final comments on EPA RCRA Toxicity Characteristic Revisions

Dear Meredith:

Enclosed is a copy of the comments we filed with the Environmental Protection Agency (EPA) on July 2, 1987 in response to the agency's supplemental proposed rule making revising the toxicity characteristic under the Resource Conservation and Recovery Act (RCRA).

We received a number of helpful comments in response to the draft we circulated on June 22, 1987. The revisions emphasize the impact that the EPA proposal would have without realizing any environmental benefits. Because some polyvinyl chloride (PVC) waste is co-disposed with municipal solid waste, we revised the comments to indicate that industrial waste is not typically co-disposed with municipal waste in landfills. In addition, our comments relating to the sampling of a sludge were deleted due to a variety of differing viewpoints on this subject within the Institute. Finally, a recommendation that EPA adopt a small quantity trigger was added so that small amounts of wastes would be exempt. A small quantity exemption would be particularly helpful for spills or other incidental discharges.

EPA has recently extended the comment period until August 16, 1987. 52 Fed Reg. 24181 (June 29, 1987). Thus, there is an opportunity to file supplemental comments on behalf

of the Institute. Naturally, individual companies can also file individual comments.

If you have any comments or questions or if I can be of any further assistance, please let me know.

Cordially yours,

Peter

Peter L. de la Cruz

cc: Robert D. Luss, Esq.
W. C. Holbrook
Joseph C. Ledvina
Charles E. O'Connell
Lewis R. Freeman, Jr.
Robert W. Sherman
Hugh Patrick Toner

Enclosure

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al studies (4, 14, 25.

Italy	
O	E
1	0.8
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3	3.0
0	1.2
1	0.8
0	0.7
1	0.9
12	6.1
0	0.2
1	0.7
1	0.7
0	0.4
0	0.7
9	4.5
30	21.1

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14, 25, 46). (O = observed

Italy	
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4	5.2
3	2.7
2	7.0
1	0.9
4	7.7
36	56.4
66	77.5

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for a total of four), but bed as an angiosarcoma

Table 3. Mortality from cancer of the liver and other causes among vinyl chloride workers in 49 plants in the four principal studies combined (4, 14, 25, 46) (O = observed number of deaths, E = expected number of deaths, SMR = standardized mortality ratio)

Cause of death	O	E	SMR
Cancer of the liver[a]	59	8.45	698
Cancer of other sites	609	599.35	102
Other diseases	1 547	1 844.89	84
Accidents, poisonings, and violence	226	295.15	77
All causes	2 441	2 747.84	89

[a] Including cancers of the gallbladder in the series from the United States.

Table 4. Mortality from various cancers among vinyl chloride workers in 49 plants in the four principal studies combined. (O = observed number of deaths, E = exposed number of deaths, SMR = standardized mortality ratio)

Type or class of cancer	O	E	SMR	Source of information[a]
Mouth and pharynx	18	16.57	81	1, 2, 3, 4
Digestive system (other than liver)	125	154.59	97	1, 2, 3, 4
Respiratory system	223	229.36	99	1, 2, 3, 4
Lung	211	214.09	111	1, 2, 4
Genitourinary system	70	62.81		1, 2, 3, 4
Melanoma	2	1.94		2, 4
Brain	29	19.54	148	1, 2, 3
Thyroid	2	0.43		2
Lymphatic and hematopoietic system	57	50.87	112	1, 2, 3, 4
Other	83	63.24	131	1, 2, 3, 4
All other than of the liver	609	599.35	102	1, 2, 3, 4

[a] 1 = United States study (14), 2 = United Kingdom study (25), 3 = Canadian study (46), and 4 = Italian study (4).

Table 5. Mortality[a] from various cancers among vinyl chloride workers: Supplementary evidence (4, 7, 22, 49). (O = observed number of deaths, E = expected number of deaths, SMR = standardized mortality ratio)

Type or class of cancer	Federal Republic of Germany (11 plants)		Norway (1 plant)		Sweden (1 plant)		Italy (1 plant)		Four countries combined (14 plants)		
	O	E	O	E	O	E	O	E	O	E	SMR
Digestive system (excluding the liver)	35.0	31.8	3[b]	1.44[b]	.	.	1	1.2	39.0	34.44	113
Lung	23.5	24.6	5	2.84	3	1.78	0	1.5	31.5	30.72	103
Melanoma	.	.	4	0.79	.	.	0	0.1	4.0	0.89	.
Brain	2.1	1.3	.	.	2	0.33	.	.	4.1	1.63	.
Thyroid	.	.	2	0.16	.	.	.	.	2.0	0.16	.
Lymphatic and hematopoietic system	16.5	7.7	.	.	.	.	0	0.7	16.5	8.4	196
Other (excluding the liver)	10.7	24.3	8	14.93	.	.	4	2.0	22.7	41.43	55
All excluding the liver	87.8	89.7	22	20.16	5[c]	2.11[c]	5	5.7	119.8	117.67	102

[a] Incidence and cases in the Norwegian study.
[b] Cancer of the intestine only.
[c] Cancer of the lung and brain only.

Further evidence that the excess mortality from liver cancer (or liver and gallbladder cancer in the US series) can be attributed principally if not wholly to the known hazard of angiosarcoma is obtained in a comparison of the excess deaths with the numbers of deaths from angiosarcomas recorded in the Register of Liver Angiosarcoma Cases (maintained on behalf of the Association of Plastics Manufacturers in Europe by the Imperial Chemical Industry PLC) before the end of the follow-up period (Bennett, unpublished). Fifty-one excess liver cancers are recorded in the combined data, and 49 angiosarcoma are recorded in the Register for

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Table 6. Mortality from lung cancer in the series from the United States (US) (14) and the United Kingdom (UK) (25) by characteristics relevant to an occupational hazard. (O = observed number of deaths, E = expected number of deaths, SMR = standardized mortality ratio)

Data characteristic[a]	Category 1			Category 2		
	O[b]	E	SMR	O[b]	E	SMR
Observed 20 years or more after first employment (1), others (2)	114	113.98	100	85	93.83	91
Employed 10 years or more in the US (1), others in the US (2)	55	52.45	105	63	63.44	99
Employed before 1956 in the UK (1), others in the UK (2)	52	51.39	101	29	40.50	72
Ever employed as autoclave worker in the UK (1), others in the UK (2)	16	17.08	94	65	74.82	87

[a] The numbers in parentheses designate the category.
[b] See footnote to table 1 for observed deaths in the US.

the relevant periods for the three countries and the two Italian plants[3] that are covered by the survey.

None of the 120 cases yet recorded in the Register were in men who were first exposed after 1969, and none of the 45 men affected in North America were first exposed after 1964. All may, therefore, have been exposed to concentrations of several hundred parts per million, and many may have been exposed to concentrations appreciably higher (unpublished report by Barr to Air Products and Chemicals Inc in 1981).

Lung cancer. The idea that exposure to vinyl chloride might cause cancer of the lung was suggested by Monson et al in 1974 (36), when they noted 13 cases against an expected number of 7.9 in a study of proportional mortality. The combined data shown in table 4 do not provide any support for the hypothesis, either for respiratory cancer as a whole (SMR 97) or for the specified data for lung cancer in the US, the UK, and Italy (SMR 99). There are, however, consistently higher risks in the subgroups of men in the US and UK series, in which occupational hazards would be more likely to be seen than in other groups. This circumstance is illustrated by table 6, which shows that the SMR values are slightly higher for men observed 20 years or more after first exposure than for men observed [illegible], for men employed before 1956 in the UK than [illegible]men first employed after 1955 (when exposure [illegible] are believed to have been lower), for men employed for longer than for shorter periods in the US, and for autoclave workers in the UK (among whom the angiosarcoma cases have mostly occurred) than for other workers. The differences are all small or very small. They are, however, all in the same direction, and the probability that the rates should all be higher in the groups in which an occupational hazard is more likely to be seen in each of the four pairs of groups is 1 in 16.

Additional information from other sources is given in table 5. A total of 30 deaths (or cases) was observed, and this figure increases to 31.5 when allowance is made for the number of deaths due to unidentified causes in the German study (SMR becoming 103). In the German study the SMR was higher for the men who had been exposed for 10 years or more than for those who had been exposed for shorter periods (111 against 79), and, in the Norwegian study, four of the five cases observed occurred in men whose occupations were regarded as involving high exposure against 1.82 of the 2.84 expected. Both the German and the Swedish studies derived the expected numbers of deaths from national mortality rates for a single year towards the end of the study period. The expected numbers of deaths are likely, therefore, to have been overestimated and the SMR values correspondingly underestimated as the mortality from lung cancer had been rising throughout the period of observation.

Brain cancer. The idea that vinyl chloride might cause brain cancer was also suggested by Monson et al (36) when they reported five cases against 1.2 expected. The combined data that are shown in table 4 provide some support for this hypothesis. The cases of Monson et al (36) were, however, observed in US workers and must be presumed to be included in the total reported by Environmental Health Associates (14); therefore they will have contributed a substantial proportion of the total in table 4. As a test of the hypothesis the data of Monson et al ought, therefore, to be subtracted from those in the table. Their investigation was not a cohort study, and their expected deaths do not correspond exactly to those in table 4. If, however, the observed and the expected cases are both subtracted from the totals, twenty-four observed deaths remain against approximately 18.3 expected, a difference which might easily occur by chance (P one-tailed = 0.1).[4]

[3] Twenty-nine were registered as occurring in the United States against an excess of 33; only 20, however, were identifiable in both series. Inquiry has, as yet, failed to reveal information about the histology of the remaining 13 in the cohort study and the origin of the nine extra deaths in the register. Nine deaths were registered as occurring in the United Kingdom against an excess of nine, but one of the registered cases was certified as due to a benign hemangioma and not related to the liver (code 227 in the eighth revision of the International Classification of Diseases). Ten cases were registered as occurring in Canada against an excess of eight; two were recorded as being in men who had been employed for five years, and it is possible that the actual duration had been slightly less than five years with consequent exclusion from the Canadian cohort. One case was registered as occurring in one of the two Italian plants against an excess of less than one.

[4] If the study of Waxweiler et al (50) is regarded as the origin of the hypothesis, 26 deaths are left against 18.94 expected (P one-tailed = 0.07).

Additional information from two other sources is given in table 5. The small excess reported provides little further evidence of an occupational hazard, as one of the two deaths observed in the Swedish study occurred in a young man who had been employed for less than a year when the diagnosis was made, while the excess death rate for brain cancer observed in the German study was less than that observed among chemical workers not exposed to vinyl chloride (2.9 deaths after allowance for deaths from unknown causes against 1.6 expected) and among workers in the PVC fabrication industry (5.9 deaths after allowance for deaths from unknown causes against 1.1 expected).

Cancers of lymphatic and hematopoietic tissues. The idea that vinyl chloride might cause cancer of the lymphatic and hematopoietic tissues — more specifically the lymphatic tissue — was suggested by Tabershaw & Gaffey (45) and by Waxweiler et al (50) in two cohort studies, when they found, respectively, five deaths from lymphomas in the most heavily exposed workers against 2.54 expected and four deaths from cancers of the lymphatic and hematopoietic tissues against 2.5 expected. These small excesses might have been ignored if the laboratory findings had not been interpreted as suggesting that lymphomas were produced experimentally in animals exposed to vinyl chloride by inhalation (29). The idea that similar exposure might also cause lymphomas in humans, therefore, merits serious consideration. The data from the four principal studies that are summarized in table 4 provide little support for the hypothesis when all cancers of the lymphatic and hematopoietic tissues are considered together (57 deaths against 50.87 expected, SMR 112) and very little more is obtained from the separate data for cancers of the lymphatic system (Tabershaw & Gaffey's definition of ICD list numbers, eighth revision, 200—203 and 205 being used) that are shown in table 1 (35 deaths against 29.40 expected). The position is, moreover, hardly altered if the data in Tabershaw & Gaffey's initial report are subtracted (29 deaths against 23.36 expected, SMR 124).

Little additional information is provided by the results of the German study (49). (See table 5.) This study obtained an SMR of 214 for exposed workers (based on 15 observed deaths, increased to 16.5 when allowance is made for the number of deaths from unknown causes) against SMR values of 77 and 34 for an unexposed group of chemical workers and a group of PVC fabricators. It showed that the excess of the exposed workers was present only for men who had been exposed for more than one year and that this excess was most marked for men who had been exposed for five years or more (10.7 deaths after allowance for the number of deaths from unknown causes against 4.0 expected, SMR 268, P one-tailed <0.01).

Melanoma. An excess of melanoma was reported for Norwegian workers by Heldaas et al (22), who raised the possibility that vinyl chloride might have produced the disease. Four cases were observed when 0.79 were expected, and three of the four were in men whose occupations involved the highest exposures (against 0.51 expected). At the time of the writing of their report, one further case had been detected with onset three years after the closure of the study. Subsequent studies in other countries have, so far, reported only two deaths against 2.0 expected. (See tables 1 and 5.)

Thyroid cancer. An excess of thyroid cancer was also reported in the Norwegian study (22), in which two cases were observed against 0.16 expected. The investigators were not aware of any other studies indicating an excess of this type of cancer; they drew no conclusion from their observation. Two of the three major studies that have been reported since the Norwegian observation was made gave no data for thyroid cancer; the third reported two deaths against 0.43 expected. (See table 1.) One death from thyroid cancer, it may be noted, was reported in the US by Monson et al (36).

Cancers of the digestive tract. Suggestions that vinyl chloride might cause cancers of the digestive tract in general have sometimes been made, but they have not taken adequate account of the contribution of cancers of the liver to the total number of cancers of the digestive system, particularly when it is borne in mind that some liver cancers are likely to be misdiagnosed as cancers of other organs. The combined data from the four principal studies shown in table 4 weigh heavily against the idea that any such effect has been produced.

Other cancers. One of the remaining types, or classes, of cancer listed in table 4 shows a statistically significant excess, namely, the heterogeneous group of "other cancers" (83 observed deaths against 65.24 expected, P two-sided <0.05). This excess is only marginally significant and may be a chance observation. The most likely explanation is, however, that a few angiosarcomas of the liver were not recognized and were diagnosed as secondary liver cancer or carcinomatosis, site unknown, the number of deaths in this category therefore being increased.

Hazards of nonmalignant disease

No previous study has suggested that any nonmalignant cause of death other than cirrhosis of the liver would be likely to be increased as a result of exposure to vinyl chloride, and cirrhosis of the liver is presumed to be increased only because of the liver changes that were observed as part of the "vinyl chloride illness" (24, 31, 33). Two other possibilities have, however, been raised, namely, the production of nonmalignant respiratory disease, because of the changes in lung function and radiographic appearances that have been

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Table 7. Mortality from selected nonmalignant causes and all causes in the four principal studies combined. (O = observed number of deaths, E = expected number of deaths, *SMR = standardized mortality ratio*)

Type of disease	O	E	SMR	Source of information[a]
Bronchitis, emphysema[b]	80	66.83	120	1, 2
Other respiratory disease	71	125.78	56	1, 2
All respiratory disease	180	200.82	80	1, 2, 3, 4
Ischemic heart disease	797	885.73	90	1,2
Other circulatory disease[c]	252	264.55	95	1,2
All circulatory disease[c]	1 103	1 209.35	91	1, 2, 3, 4
Cirrhosis of the liver	46	66.26	69	1, 2, 4
Other disease	238	368.07	65	1, 2, 3, 4
All nonmalignant disease	1 547	1 844.50	84	1, 2, 3, 4
All external causes	226	295.15	77	1, 2, 3, 4
All nonmalignant causes	1 773	2 139.65	85	1, 2, 3, 4
All causes	2 441	2 747.85	89	1, 2, 3, 4

[a] 1 = United States study (14), 2 = United Kingdom study (25), 3 = Canadian study (46), and 4 = Italian study (4).
[b] Bronchitis in the United Kingdom study, emphysema in the United States study.
[c] Includes cerebrovascular disease in the United Kingdom and Italian studies.

Table 8. Mortality from chronic obstructive lung disease[a] in the series from the United States (US) (14) and the United Kingdom (UK) (25) by characteristics relevant to an occupational hazard. (O = observed number of deaths, E = expected number of deaths, SMR = standardized mortality ratio)

Data characteristic[b]	Category 1			Category 2		
	O	E	SMR	O	E	SMR
Observed 20 years or more after first employment in the US (1), others in the US (2)	30	15.8	190	11	7.0	157
Employed 10 years or more in the US (1), others in the US (2)	16	10.9	147	25	12.0	208
Employed before 1956 in the UK (1), others in the UK (2)	26	30.17	86	10	13.60	74
Ever employed as an autoclave worker in the UK (1), others in the UK (2)[c]	3	6.55	46	33	37.22	89

[a] Described as emphysema in the US study and as bronchitis in the United Kingdom study.
[b] The numbers in parentheses designate the category.
[c] Men ever employed as a bagger or drier, occupations which would have caused the greatest occupational exposure to polyvinyl chloride dust, experienced one death from bronchitis against 4.98 expected.

recorded for men exposed to PVC dust (2, 26, 27, 44), and acute cardiac death, from analogy with the effect of other halogenated hydrocarbons (25) and the observation of an increased mortality from myocardial infarction in the few years following the cessation of exposure in the Swedish PVC processing industry (35). Relevant figures for the numbers of deaths from these and other nonmalignant causes that are obtainable from the four principal studies were given in table 2, and they have been summarized in table 7.

Cirrhosis of the liver. Three of the four principal studies gave separate figures for cirrhosis of the liver, none of which showed an increased mortality (table 2); in combination they gave an SMR of 69 based on 46 deaths. The fourth study, which did not give separate data for cirrhosis of the liver, reported four deaths from all diseases of the digestive system combined against 3.85 expected and noted that the four included two that were certified as due to cirrhosis of the liver, but actually due to angiosarcoma (46). In the two supplementary studies in which data were given for this disease, the SMR was 82 in one, based on 15.1 deaths after allowance for the number with unknown causes (49), and 133 in the other, based on seven deaths (37).

Nonmalignant respiratory disease. The data for nonmalignant respiratory disease are confusing in that the total SMR from the combined data for the four principal studies is 80 and is the sort of figure that is commonly found in healthy industrial populations, yet the US study recorded a substantially increased mortality from emphysema (41 deaths and an SMR of 180 before any allowance was made for deaths from unknown causes). No such excess was found in the UK, where 36 deaths from bronchitis gave an SMR of 82. International comparisons of chronic nonmalignant respiratory disease are complicated by the usage of different terms to describe what it is now agreed is best called chronic obstructive lung (or pulmonary) disease, but which in the past tended to be called emphysema in the US and chronic bronchitis in the United Kingdom. It must, therefore, be presumed that the two categories of "emphysema" and "bronchitis" used respectively in the two large national studies were meant to describe the same thing. One must assume, therefore, that the experiences in the two countries were very different, despite the fact that both related to cohorts that had very similar experiences of angiosarcoma of the liver and so, presumably, fairly similar exposures to vinyl chloride.

Separate figures are shown in table 8, where available, for the mortality observed among men with different durations and intensities of exposure. Unlike the data for cancer of the lung that were shown in table 6, they provide no consistent evidence of a greater risk in the groups in which an occupational hazard would

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...be expected to be concentrated. The authors of the Environmental Health Associates report (14) were unable to give any explanation for the increased mortality from emphysema, and they point out that it could possibly be due to excess cigarette smoking, as there was no overall excess for cancer of the lung. It is striking, however, that the excess is more than compensated for by deficiencies in the other categories of nonmalignant respiratory disease (pneumonia 15 deaths,[3] SMR 47.0; other respiratory disease 14 deaths, SMR 42.6), and the question arises whether the emphysema excess could be a classificatory artifact. Environmental Health Associates (14) list all the 41 deaths which show that they were coded under ICD number 527 which, in the out-of-date seventh revision that was used for the coding of all deaths in the study, was the code for "other respiratory disease not otherwise classified" and included emphysema. Under that revision, however, emphysema that was associated with bronchitis should be classified with bronchitis under ICD numbers 500 to 502, and the possibility may be considered that some of the emphysema deaths should have been classified in some category of respiratory disease other than ICD number 527. If this were the situation, it could account for both the excess mortality from emphysema and the previously deficient mortality from other nonmalignant respiratory diseases.

No excess mortality from "bronchitis, emphysema, and asthma" was observed in the German study (SMR 88 with 6.3 deaths observed after allowance for the number of deaths from an unknown cause) (49).

Cardiovascular disease. Data for ischemic (or arteriosclerotic) heart disease (which may be presumed to include the vast majority of all deaths certified as due to acute cardiac disease) were given only by the two occupational studies, and they provide no evidence of an increased mortality. The SMR values of 90 for this group of diseases and of 91 for all cardiovascular diseases recorded in the four principal studies are typical of the SMR values of healthy industrial populations, and there is no suggestion of any occupational hazard in the subsidiary analyses provided by the two national studies. In particular, there is no evidence of an increased mortality within one month of leaving employment in the UK study either for all workers (52 deaths, SMR 61) or for the most heavily exposed autoclave workers (9 deaths, SMR 42).

A slight increase in ischemic heart disease mortality was recorded for the exposed workers in the German study (49), but it was less than that recorded for the unexposed chemical workers and the PVC fabricators (SMR values of 127, 131, and 158 based on 97.2, 126.7, and 109.7 deaths, respectively, after allowance for the number of deaths from unknown causes).

[3] The deaths attributed to different groups of respiratory diseases and the corresponding SMR values that are cited in this section for the US study are as given by the Environmental Health Associates (14) and have not been adjusted in any manner for the number of deaths from an unknown cause. To take account of these deaths, the observed deaths and SMR values can both be multiplied by 1.0674.

Discussion

The information that has now been obtained about the long-term health of men occupationally exposed to vinyl chloride is massive and compares favorably with that available for any other occupational group. Two facts are outstanding. First, the men have experienced a specific hazard of a type of cancer that is normally extremely rare, namely, angiosarcoma of the liver. The rarity of this disease under other conditions made the detection of the hazard easy; but the long latency period before the disease appears after first exposure (almost always more than 10 years and usually more than 15 years) meant that a large number of men had been exposed before the hazard was detected and that it will still be many years before the extent of the protection provided by the reduction in exposure in the 1960s and that of the further reduction that followed the recognition of the hazard in 1974 are known. There is, unfortunately, no effective treatment for the disease, and the number of cases is reflected in the number of deaths. Some 50 deaths have occurred among the 16 740 men who were followed in the four principal studies that have been reviewed in this report, so that approximately 1 in 335 men have been affected, 2 % of the deaths having been due to this one cause. Eventually many more men must be expected to develop the disease. One estimate (38) suggests that the total may be increased 10 times, but a more realistic estimate is two to three times (19).

The second outstanding observation is that the mortality of the exposed men, other than that due to angiosarcoma of the liver, is typical of the normally healthy industrial worker — that is not to say that no other hazard exists, but that the effect of any other hazard is small.

The massive data that are now available provide no reason for thinking that any hazard other than one of cancer has been overlooked. It is, however, still difficult to decide whether vinyl chloride produces a risk of developing cancer other than angiosarcoma of the liver which might be small compared to the risks produced by nonoccupational causes, but yet absolutely almost as large as the risk of developing the normally very rare angiosarcoma.

One of the many hazards suggested can be dismissed, as there is no evidence to support it, namely, that of vinyl chloride as a cause of any cancer of the digestive tract other than angiosarcoma of the liver. Two hazards (of melanoma and cancer of the thyroid) have been suggested only very recently, and few of the available studies have provided information about them. There is no good theoretical reason or laboratory evidence to suggest that either should be produced by

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vinyl chloride, and, in light of present evidence, the simplest explanation is that the reported excesses are the chance effects that must be expected when many different types of cancer are studied in several different populations. So far as melanoma is concerned, it has to be remembered that the disease has become much more common in recent years in Scandinavia (where the excess was reported) due, it is believed, to the popularity of sunbathing and the increased opportunities for Scandinavians to travel to the warmer parts of Southern Europe and North Africa. The extent to which this change may have affected the observation in Norway needs to be examined.

Two other hazards (of lymphoma and brain cancer) were suggested by the early results of some of the US studies. That vinyl chloride might produce a hazard of lymphoma was initially supported by the preliminary results of animal studies, but the complete results of the many investigations that have been undertaken (see reference 29) do not suggest that lymphoma or any other cancer of the hematopoietic system is liable to be produced. There is, however, some evidence that brain tumors can be produced in rats (29). The hypotheses that lymphomas and brain cancers might be produced by vinyl chloride have been supported by the observation that both these types of cancer have caused death more often than might be expected from national mortality rates, but the excesses observed in the combined data from the four principal studies in this review are small and not statistically significant, and the hypotheses remain unproved. The small excess of brain cancer is particularly difficult to evaluate, as mortality rates from this disease have changed rapidly over time as methods of diagnosis have improved and the suspicion of an occupational hazard (which was raised in 1975) could have influenced the findings. What excess has occurred has been limited to the US and Germany, and the German findings carry little weight, as the excess was found in each of the three occupational groups studied, irrespective of the chemicals to which they were exposed. The supplementary data from the German study showing an increased mortality from lymphatic and hematopoietic cancers are more impressive, particularly as the excess was the most marked for men who had been employed for at least five years. In these circumstances, judgment must still be suspended until the data for each study are analyzed for each specific type of cancer, by intensity and duration of exposure, and by time since exposure began.

There remains the suggestion that vinyl chloride might cause lung cancer. At first sight, this possibility is ruled out by the SMR of 97 for the combined data for respiratory cancer for the four principal studies. Lung cancer is, however, normally so common (accounting for about 8 % of the expected deaths) that an increase in mortality that was half as important (numerically) as the increase in mortality from angiosarcoma of the liver might easily be overlooked (95 % confidence limits of the SMR 85—112). The incidence of the disease varies moreover within a country, and there must be doubts as to whether the national experience provides a suitable reference for men employed in plants that are not evenly distributed about the country. In these circumstances one cannot exclude an occupational hazard unless it can be shown that the mortality of the exposed men is independent of the factors that might be expected to influence it if some of it were occupational in origin, namely, the intensity and duration of exposure and the time since exposure began. It is not possible to examine these relationships in detail, as the reports do not provide all the necessary information. Such information as they do provide, which was summarized in table 6, supports the idea that exposure to vinyl chloride involves a small hazard of lung cancer. Taken in conjunction with the knowledge that lung tumors have been produced in several species of animals exposed to vinyl chloride by inhalation (29), it would seem that a small hazard of lung cancer probably did occur. The evidence is not, however, strong enough to conclude that it definitely did. If it did, the hazard was evident only for men who had been employed for many years at a time when exposures of several hundred parts per million or more were common, and any persisting risk can be only minute and incapable of detection.

The questions that have been left unanswered by this discussion might well be answered definitely if (i) all the exposed men could be followed to (say) the end of 1984, (ii) the investigators could present their data in comparable ways, taking account of duration of employment and time since first employment and presenting data separately for men first employed before (say) 1965 and between 1965 and 1974, and (iii) estimates could be made of the effect of correcting the results for each group of employees for the locality in which they lived and worked.

Hazards to the general population

As vinyl chloride has been proved to cause cancer in man and is a mutagen in laboratory experiments, it must be presumed that even the minute doses that escaped into the general environment from production plants or (in the early days of manufacture) from PVC materials will have caused some risk of cancer to the general public. These risks must, however, have been very small, as air concentrations of vinyl chloride, even within a kilometer of plants handling vinyl chloride, used to be (in or around 1975) of the order of 10 to 40 ppb (1, 3, 15), and this level is about one-ten thousandth of the concentration that has caused an occupational hazard. It is obvious, therefore, that it would be impossible to detect the risk of any cancer that might be produced by vinyl chloride other than a risk of angiosarcoma of the liver, as it has proved so difficult to detect any other risk among men who were exposed occupationally. The position with regard to an-

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giosarcoma of the liver is different. This disease is normally so rare that, in the absence of specific exposure to one of the known causes (vinyl chloride, thorium dioxide, and arsenic in pesticides and medicines), the annual incidence is on the order of $1—2 \cdot 10^{-7}$ (5, 8).[4] In these circumstances the discovery of even one case in a man living close to a factory in which vinyl chloride was used in the days before exposure was tightly controlled may be regarded as presumptive evidence of the effect of environmental pollution.

Several surveys have been undertaken to determine whether any such cases have occurred. Saric et al (43) and Elinder & Pershagen (13) sought for cases in the vicinity of plants handling vinyl chloride in Yugoslavia and Sweden and found none. In Holland Dalderup et al (11) found eight confirmed cases not attributable to thorotrast or arsenic and could trace "no contact with vinyl chloride," but they made no specific mention of the patient's place of residence. Baxter et al (3) found 14 confirmed cases in Great Britain over a 12-year period, one of which was in a man who had lived half a kilometer from a PVC manufacturing plant, and, in New York State over an 18-year period, Brady et al (5) found 19 cases that could not be attributed to any known cause, five of which were in people living within a mile of plants manufacturing or using vinyl chloride. The overall incidence rates in these last two studies were not unduly high, but the occurrence of as many as six cases among people living so close to manufacturing plants is surprising. Brady and his colleagues, moreover, compared their series of patients with matched referents and found that none of the referents lived equally close to a plant. Two of these six neighborhood cases (one in England and one in New York State) cannot be attributed to environmental pollution with vinyl chloride, as the men who developed the disease had lived near the plants for six and eight years, respectively, before developing the disease, and this period is too short to allow for the necessary latency. The other four cases, however, all occurred after 15 or more years of local residence, and the discovery of these cases strongly suggests that pollution of the environment around plants manufacturing VCM or PVC may have caused a minute hazard to the general public.

Current concentrations around plants handling vinyl chloride are certainly much lower than those reported previously by the US Environmental Protection Agency. Recent British measurements made within a few hundred meters of the VCM areas have given average values below the daily limit of detection (5 ppb) for three of five plants, the readings at the two others being 20 ppb (100 m outside the boundary fence) and 88 ppb (just inside it) (47), although substantially higher values were recorded on two occasions associated with putting one plant into operation and with an accident at the other. According to any reasonable criterion the hazard to the general public (if there is any at all) must be negligible (42).

No other hazard to the general population, other than a hazard of cancer, can reasonably be postulated.

[4] The figure of $1.4 \cdot 10^{-8}$ cited by Heath et al (21) seems to have been a misprint for $1.4 \cdot 10^{-7}$.

Summary

This paper reviews (i) the possible effects of vinyl chloride on the personal health of men exposed by virtue of their occupation (other than the early effects of the very high concentrations to which men were exposed when the industry was first developed — unconsciousness, cardiac arrhythmia, and the characteristic "vinyl chloride illness") and (ii) the carcinogenic effects that might conceivably be observed in the general population as a result of the widespread distribution of vinyl chloride as a pollutant. The possibility that vinyl chloride might act as a teratogen or might cause mutations in the germ cells has not been examined, as the little evidence that has been adduced relating to such possible effects has been reviewed elsewhere and the conclusion was reached that no such effects have been demonstrated.

Many groups of workers exposed to vinyl chloride in the manufacture of VCM or PVC have been studied since the carcinogenic potential of vinyl chloride was first recognized. Some results have shown that occupational exposure can cause angiosarcoma of the liver, and others have suggested that it may cause several other types of cancer as well. The actual situation can be determined only in an examination of all the evidence, especially the combined results of those studies that include a substantial proportion of observations on men more than 25 years after their first exposure and cover a long enough period for more than 10 % of the employees to have been expected to die.

The results of four studies can be usefully combined for this purpose. They are two national studies, one from the US and the other from the UK, and two studies of employees in one plant in Canada and two plants in Italy. The results of other studies from the Federal Republic of Germany, Norway, Sweden, Italy, France, and Japan can be used only to provide supplementary information. The many earlier reports of exposed workers in the US and the UK concern men covered more completely in the two recent national studies, and their results serve only as sources of hypotheses.

Minor criticisms can be made of three of the four most useful studies. They do not seriously affect the value of the results, except that allowance has to be made for the failure to determine the cause of 6.3 % of the deaths recorded in the US study. Three of the studies use national rates to estimate the numbers of deaths that might have been expected to occur in the absence of any special occupational hazard, and the fourth (Canadian) uses rates for the province in which

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the plant was situated. It must, therefore, be kept in mind that the rates used may not have been wholly appropriate for the localities in which the plants were situated. This circumstance is potentially important for the US study, which covered workers in 37 plants, 22 of which were situated in the southern part of the country. The other less informative studies are, for the most part, open to more serious criticism, and the value of each set of results needs to be assessed separately in relation to each disease.

The combined results of the four principal studies show that the SMR values, reflecting the ratios between the numbers of deaths observed and those expected in the absence of an occupational hazard multiplied by 100, have been (i) 77 for accidents and other violence, (ii) 84 for diseases other than cancer, and (iii) 102 for cancers other than cancer of the liver. All these results are what might be anticipated for an industry devoid of any specific occupational hazard. The low ratio for diseases other than cancer reflects the "healthy worker effect," which results from the selection process that inevitably excludes some of the less healthy members of the population from industrial employment and is compatible with a higher ratio for cancer, as the mortality from cancer is not normally subject to such an effect, apart from the first two or three years immediately following the start of employment.

The mortality from cancer of the liver was nearly seven times that expected. Most of the 51 excess deaths were known to be due to angiosarcoma, even though this diagnosis was not recorded on the death certificate. The excess corresponds closely with the 49 deaths due to angiosarcoma reported to the International Register of Angiosarcoma Cases as occurring in employees of the plants concerned during the periods under observation. All the men who developed the disease were likely to have been exposed to concentrations of vinyl chloride of several hundred parts per million or more.

Three other types of cancer which have been suggested to occur as a result of exposure to vinyl chloride are cancers of the lung, brain, and lymphatic and hematopoietic systems. The combined data for the mortality from respiratory cancer fail, at first sight, to support the hypothesis regarding lung cancer (SMR 97). Higher ratios for lung cancer have, however, been observed consistently in the subgroups in which the effect of an occupational hazard would be most likely to be seen (that is, men employed for more than 10 years, exposed to higher than average concentrations, or observed more than 20 years after first exposure). In two of the supplementary studies it was also noted that the mortality from lung cancer was specifically increased among the most heavily exposed workers. The combined data show small excesses in the mortality from cancers of the brain and of the lymphatic and hematopoietic systems. The excesses are, however, not statistically significant, and there is nothing to suggest that they are occupational in origin. An exception is the observation of an increased mortality from cancers of the lymphatic and hematopoietic systems in the supplementary study from the Federal Republic of Germany.

Two types of cancer were reported [illegible] in excess in the Norwegian study, namely, [illegible]ancer and melanoma. The significance of this finding is difficult to assess because very little information about these cancers has been provided by other studies.

Suggestions that vinyl chloride might cause cancers of the digestive tract have failed to account for the contribution of angiosarcoma of the liver. When this disease is excluded, the mortality from digestive tract cancer decreases to below the average (SMR 82 for the four principal studies).

A small excess mortality from the heterogeneous group of "other cancers" in the combined results of the four principal studies was statistically marginally significant (83 deaths against 65.25 expected, $P < 0.05$). Some of the excess was likely to have been due to the misclassification of angiosarcomas as secondary cancers of the liver or carcinomatosis, site unknown.

The following three nonmalignant causes of death have required special examination: cirrhosis of the liver because of damage to the liver in "vinyl chloride illness," myocardial infarction (from analogy with the effect of other halogenated hydrocarbons and because of some observations from Swedish PVC fabricators), and nonmalignant respiratory disease because of changes in lung function and the radiographic appearance of the lungs observed in men exposed to PVC dust. Far from being raised, the mortality from cirrhosis of the liver was less than expected in the three principal studies and in one of the two supplementary studies which gave separate figures for the disease (SMR values of 69, based on 46 deaths, and 82, based on 15 deaths), while in the other supplementary study the increase was trivial.

Data for myocardial infarction have not been reported separately. But myocardial infarction accounts for most of the deaths attributed to ischemic heart disease, and there is no evidence that either ischemic heart disease or cardiovascular disease as a whole was unduly common (SMR values of 90 and 92, respectively) or related to occupational exposure.

The data for the third category of nonmalignant disease (nonmalignant respiratory disease) are confusing, because the two large national studies give conflicting results. The combined data for the four principal studies show the low mortality that is commonly found in healthy industrial populations (SMR 80). This figure hides, however, an increased mortality from chronic obstructive lung disease (SMR 120), which includes emphysema and is due to a grossly increased mortality attributed to emphysema in the US study (SMR 193). The corresponding mortality in the British study, which was preferentially described as due to bronchitis, was less than expected (SMR 82), as was the mortality from pneumonia (SMR 50) and other res-

piratory diseases (SMR 46) in the US study. There is no consistent evidence that the mortality from emphysema or bronchitis was specifically occupational, and it seems possible that the reported excess in the US study was an artifact due to nosological difficulties with the use of the seventh revision of the ICD.

Review of the massive data now available on the long-term health of men occupationally exposed to vinyl chloride leads to two clear conclusions. First the men have experienced a specific hazard of the normally extremely rare angiosarcoma of the liver. Approximately 1 in 335 of the men exposed in the 49 plants studied died of the disease, and approximately 2 % of the observed deaths were attributed to it. In the course of time the numbers of cases of angiosarcoma must be expected to increase two to three times. Second, the mortality from all other causes has been typical of that of normally healthy industrial workers. If any hazard has existed, its effect has been small.

The data provide no reason to think that any hazard other than one of cancer has been overlooked. It is, however, still difficult to decide whether vinyl chloride produces small risks of cancer, compared to those due to nonoccupational causes, at sites other than the liver, and, if so, whether, in total, these risks might cause almost as many deaths as angiosarcoma of the liver.

There is too little evidence either to confirm or refute the suggestion that vinyl chloride might cause melanoma or cancers of the thyroid, brain, and lymphatic and hematopoietic systems. None of the small excesses that have been recorded point specifically to an occupational hazard, apart from that attributable to cancers of the lymphatic and hematopoietic systems in the German study reviewed, and most are likely to be the sort of chance effect that is certain to be observed when many types of cancer are examined in many different studies.

The lack of any increased mortality from lung cancer in the combined results of the four principal studies reviewed does not exclude the possibility that there may have been a small occupational hazard of developing the disease, as geographic variations in the incidence of the disease throw doubt on the validity of using national rates for estimating the expected numbers of deaths. The greater mortality in groups of workers who would be more likely to show an occupational hazard than other groups suggests that a small hazard may have existed. The evidence is, however, weak, and the existence of a hazard has not been proved.

Clearer answers to some of the questions that have been posed in this review might be obtained if the various groups of investigators could present their results in more appropriate and comparable ways.

As vinyl chloride is a mutagen in laboratory experiments and a proved human carcinogen, the minute doses that have escaped into the general environment as pollutants must be presumed to have caused comparably minute risks to the general public. No such risk could possibly be detected, other than one of angiosarcoma of the liver which is normally an extremely rare disease. Several surveys have sought evidence of the existence of such an effect, and suggestive evidence that such an effect may have occurred at a time when environmental pollution was much greater than it is now has been found in one.

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