QUANTITATIVE RISK ASSESSMENT FOR COMMUNITY EXPOSURE TO VINYL CHLORIDE

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EXECUTIVE SUMMARY

Vinyl chloride has produced liver angiosarcoma, a very rare form of cancer, as well as other cancers and serious liver damage in occupationally exposed populations. Since it is generally considered prudent to assume that there is no threshold for chemical carcinogens, the small concentrations of vinyl chloride observed in the ambient air in the vicinity of plants producing vinyl chloride monomer (VCM) or polymerizing it to polyvinyl chloride (PVC) involve some public health risk. This paper reports the results of an analysis to estimate quantitatively the risk resulting from vinyl chloride emissions and assess the reliability of the estimates. In addition, a search was initiated of the residence of people who have died of liver angiosarcoma in order to detect evidence of adverse effects among people living near plants.

The analysis involves three steps: estimation of the number of people exposed, the concentrations of vinyl chloride to which they are exposed, and the number of cancers and other health effects resulting from this exposure. Of these, the last is by far the most difficult to make and involves the most conceptual problems.

The number of people living at various distances from each VCM and PVC plant was determined by an analysis of census data. All told, some 4.6 million people live within 5 miles of these plants.

Ambient concentrations of vinyl chloride in the vicinity of plants were determined using standard methods of diffusion modeling. Exposures at each location were adjusted to allow for the types, numbers and sizes of plants present and the meteorological conditions which affect the dispersion of pollutants. It was found that the 4.6 million people living within 5 miles of uncontrolled VCM or PVC plants are exposed to an average concentration of about 17 parts per billion.

Quantitative estimates of health effects likely to result from this exposure were made by predicting from animal data the probability that highly-exposed workers would get angiosarcoma, checking that prediction by calculating the same probability using epidemiological studies of workers, and then projecting the results to ambient concentrations around plants. Cancers other than liver angiosarcoma were assumed to occur at the same relative rate as at the higher doses. Birth defects have been reported in communities with VC and VCM plants. These effects are not considered in detail here because quantitative estimates of these effects can not be made at this time.

Projections from incidence rates in rats to incidence rates in highly-exposed workers were made by assuming that a lifetime exposure to rats would produce the same number of effects as a lifetime of exposure to humans, which means roughly that one year of exposure to rats yields the same incidence rate as 30 years of exposure to people.

It was found, using a linear dose-response model extrapolating to zero, that the probability of getting angiosarcoma due to a year of continuous exposure is 71 cases per year of continyous exposure per ppm of vinyl chloride per million people exposed. The corresponding probability of getting cancer of all sites is 150 cases per year of continuous exposure per per ppm of vinyl chloride per million people. On this basis the probability of getting liver angiosarcoma in workers exposed to 350 ppm for 7 hours per day, 5 days per week would be 0.0052 per person per year of exposure.

From epidemiological studies of exposed workers, it was estimated that the probability of getting angiosarcoma at some time in the worker's life per year of exposure is 0.0031. To arrive at this rate, the analysis considered the distribution of exposure durations among the 14 known occupational cases of angiosarcoma, as well as the time distribution of man-years of exposure in the industry. Two other important facts about vinyl chloride carcinogenesis resulted from this analysis: 1) at some time in their lives about 7.5% of all highly-exposed workers are expected to get liver angiosarcomas due to vinyl chloride exposure with double this rate of primary cancer at all sites combined. 2) Of all the cases of liver angiosarcoma which have this far been produced by vinyl chloride, only 38% of them have been diagnoses as of 1974.

After considering the error associated with the separate estimates based on animal and human data, it is concluded that the two approaches give results that are indistinguishable.

The projection to low doses was done using two separate mathematical models of the animal data: 1) the linear model, which assumes that the response rates are directly proportional to dose with no threshold; 2) the log-probit model, which assumes that the susceptibility of the population is log-normally distributed with dose. The former model is widely used for low-dose extrapolation in radiation carcinogenesis and is generally considered to be conservative for chemical carcinogens, and the latter is usually used for describing the dose-response relationship in the dosage range of animal experiments.

It was found that the rate of initiation of liver angiosarcoma among people living around VCM-PVC plants is expected to range from less than one to ten cases of liver angiosarcoma per year of exposure to vinyl chloride. The log-probit model gives predictions that are 0.1 to 0.01 times this rate. This wide range is an indication of the uncertainties in extrapolation to low doses. The cases initiated by exposure this year will not be diagnosed until 1991 or 1995. Vinyl chloride is also expected to produce an equal number of primary cancers at other sites, for a total of somewhere between less than one and twenty cases of cancer per year of exposure among residents around plants. The number of these effects is expected to be reduced in proportion to the reduction in the ambient annual average vinyl chloride concentration, which is expected

to be 5% of current levels after the proposed EPA regulations are implemented.

As part of this analysis a survey of the known cases of liver angiosarcoma diagnosed in the last 10 years was initiated in order to see whether any evidence could be found that living near VCM or PVC plants results in higher rates than expected for the general U. S. population. No conclusion can be drawn from the survey at its present stage of completion. It is expected that if the true rate is as high as 10 cases per year of exposure among residents near plants, which is the highest rate our analysis would predict, higher than average rates of case occurrence might not yet be observable in such a survey but should become detectable in the next 5-10 years, due to the increase in vinyl chloride production rates since 1955-1960.

Table of Contents

Quantitative Risk Assessment for Community Exposure to Vinyl Chloride

Vinyl chloride is a known human carcinogen; it has produced liver angiosarcoma, a very rare form of cancer, as well as other cancers and non-cancer effects in occupationally exposed populations. It is also known to be emitted into the atmosphere from plants which produce vinyl chloride monomer (VCM plants) and plants with polymerize the monomer to polyvinyl chloride (PVC plants). Although concentrations of vinyl chloride in the ambient air are much less than those which caused cancer in workers, it is generally considered prudent to assume that there is no threshold for chemical carcinogens, so that any exposure involves some risk. In conjunction with EPA consideration of rulemaking action to regulate emissions of vinyl chloride from VCM and PVC plants, the Administrator of EPA requested that an analysis be performed which would estimate quantitatively the risk resulting from VC emissions and assess the reliability of the estimates. This paper reports the results of that analysis. The details are presented in the Appendices A through E.

The analysis involves three steps which are discussed in turn below: an estimate of the size of the exposed population, an estimate of the concentrations of vinyl chloride to which they are exposed, and an estimate of the number of liver angiosarcomas and other health effects which would result from this exposure. Of these, the last estimate is by far the most difficult to make. In addition an investigation was made of the places of residence of all people known to die of liver angiosarcoma in the last ten years in an attempt to detect clustering around PVC and VC plants.

Size of exposed population

A study by the American Public Health Association (APHA), performed under contract to EPA's Office of Toxic Substances, determined the number of people living within various distances, up to 5 miles, from each VCM or PVC plant. The study was based primarily on census tract information. The validity of the methodology used was confirmed by a more detailed analysis of the population living around a few plants, performed by EPA's Office of Planning and Evaluation.

The total population living within 5 miles of all PVC and VCM plants is shown in the following table:

Distance (mi)	Population
0 - 1/2	47,000
1/2 - 1	203,000
1 - 3	1,491,000
3 - 5	2.838,000
TOTAL	4,579,000

Thus, a total of 4.6 million people live in the vicinity of these plants. To calculate the average exposure, detailed population data around each individual plant was weighted to reflect differences in the type of plant (PVC or VCM), size of plant (average or large) and meteorological conditions at the plant site.

The use of residence data involves some error, of course, since people spend part of their time away from their homes and hence exposed to varying levels of vinyl chloride. There does not seem to be any practical way around this problem, short of a detailed study of travel patterns of 4 million people in over 40 separate communities.

Ambient vinyl chloride concentrations

Annual average ambient concentrations of vinyl chloride were calculated by standard diffusion modeling techniques. Two independent studies were made, one by EPA's Office of Air Quality Planning and Standards (OAQPS) and one by Teknekron, Inc. The agreement among the two studies was good, with differences generally less than 25%. It was decided to use the Teknekron results in the actual calculations since they included data on variations in meteorological conditions from location to location.

For an average uncontrolled PVC or VCM plantin an area with average meteorological conditions, the annual average concentration of vinyl chloride in each annulus around the plant is shown in the following table:

Distance (mi)	Vinyl chloride concentration (ppb)	
	PVC plant	VCM plant
0 - 1/2	323	113
1/2 - 1	57	20
1 - 3	15	5.2
3 - 5	5.7	2.0

It can be seen that concentrations around VC plants are significantly smaller than around PVC plants. This fact combined with the much smaller population living near VC plants, implies that by far the greatest part of the public health risk is from emissions from PVC plants.

In calculating total population exposure, it is necessary to take account of factors that lead to variations from the average. Information from OAQPS and from the APHA study was used to determine areas where more than one plant was located, and OAQPS characterized the size of each plant as "average" or "large." The Teknekron study was used to categorize the meteorological and topographic conditions at each location. Details are given in Appendix A.

The net result of these calculations is that the average exposure faced by a person chosen at random from the 4.6 million people living within 5 miles of plants is 17 ppb.

Unfortunately, it has not been possible to make a systematic comparison of the diffusion modeling results with data obtained from actual monitoring, although they appear generally consistent. It is therefore difficult to estimate the uncertainty of these estimates. Lacking anything better, we can take the difference between the two diffusion modeling efforts of up to 25% as an estimate of that uncertainty.

Health effects resulting from exposure

What are the results of exposing 4.6 million people to an average of 17 ppb of vinyl chloride? The first major decision to face in answering this question is to arrive at some combination of two basic approaches. One approach is to rely largely on human data (which exists for vinyl chloride but not for many other chemicals of concern to EPA): the secons is to make projections from animal experiments. Both involve difficulties. Use of human data eliminates the uncertainties that result because we do not know the differences in response between the test animals and humans. On the other hand, with the data on human (occupational) exposure, it is necessary to guess at exposure levels over the past 30 years and approximate the total number of workers involved and the number of cancers caused by past exposures for which symptoms may not appear until many years in the future. By using animal data we can avoid these problems, but only at the price of uncertainty in the relevance of animal experiments to human exposures. The approach taken in this analysis is to use animal data to predict the probability of human liver angiosarcoma, and then use the human data to the greatest extent possible to interpret those predictions.

A second major decision that must be made is how to project the results observed at high doses in animal experiments (and in the occupational exposures) to the much lower doses encountered in the environment. Two alternative assumptions are frequently made in the scientific literature. The first is a straight-line projection to zero dose, assuming no threshold (the "linear model"). This is also referred to as the "one hit" model, since it would follow logically from the assumption that each minute increment of exposure to a carcinogen has the same independent probability of causing a cancer, regardless of the dose level. This assumption is generally accepted as prudent in radiation carcinogenesis. For chemical carcinogenesis, the model is usually considered to provide an upper limit to the level of effects likely at extremely low doses, because the existence of detoxification mechanisms would render small doses less effective in causing cancer and would therefore result in a threshold of at least fewer effects.

The second commonly used projection method is based on the assumption that the observed changes in response with dose are the result

of variations of susceptibility in the population, which is assumed to be log-normally distributed with dose. For convenience, we refer to this as the "log-probit" model because it forms a straight line when the logarithm of the dose is plotted against the proportion of responses expressed in probability units (probits). The log-probit model is closely related to the Mantel-Bryan procedure.

In this analysis, both models are used. For technical reasons, the log-probit model is difficult to apply to this case. Therefore, the basic calculations were done using the linear model, but a sensitivity analysis was done to show how the results would change under the log-probit assumption.

A third decision that must be made is how to predict human incidence rates from animal data. Again, there is little hard data to provide guidance. The assumption used here is that a lifetime exposure of humans to a given concentration of vinyl chloride would produce the same number of effects as a lifetime exposure of rats. Thus, the one-year exposure in the animal experiments would be equivalent to about 30 years of exposure for humans.

A fourth decision to make is how to use the available human data on liver angiosarcoma cases among highly-exposed workers to calculate the probability per year of exposure that cases will eventually develop in people. This calculation is needed for comparisons with the animal model. There are three aspects to this problem: 1) to find in the literature a realistic estimate for the fraction of highly-exposed workers who have contracted liver angiosarcoma at some time in their lives; 2) to account for the fact that the currently-observed rates underestimate the actual incidence because they do not include workers who have been exposed more recently than 15 to 20 years ago; and 3) to account for the fact that people can die from other causes before a latent case of liver angiosarcoma becomes manifest.

These issues were treated as follows: Of the four occupational epidemiology studies from which it is possible to estimate an incidence rate, the two with the smallest number of subjects and the best separation of highly-exposed workers from the group of all workers had the largest incidence of angiosarcoma. This incidence was assumed to be valid for all highly-exposed workers. The latency time for liver angiosarcoma and the growth in the number of person-years of exposure since 1940 are two factors which affect the number of cases we have observed through 1974. These factors, along with the distribution of exposure durations for people who have been diagnosed with liver angiosarcoma, were included in an analysis presented in Appendix D. The result of the analysis is an estimate of the probability per year of exposure that a person will get angiosarcoma sometime in his life. The remaining problem of multiple risks competing for mortality was not treated because of its complexity.

A fifth decision which had to be made was how to quantatively describe the other effects of vinyl chloride exposure besides liver angiosarcoma. This problem was handled by estimating from the literature ratios of the number of people with other cancers and the number of people with liver damage compared to the number with angiosarcoma. As an index of liver damage, the bromsulphalein (BSP) test is used because it, among all liver function tests that have been used, correlates best with vinyl chloride exposure and because an abnormal BSP test indicates that severe damage has occurred in the liver, either because the liver cells are not able to assimilate the intravenously injected BSP dye from the blood and excrete it into the bile passages, or that the bile passages are no longer structurally intact enough to carry the dye out of the liver.

The results of these five aspects of the problem are presented below in reverse order. The approximate ratio of severe liver damage cases to liver angiosarcoma cases is about 30, the result being consistent for two independent occupational studies. It was also found that about twice as many cases of cancer of all sites are caused by vinyl chloride as cases of liver angiosarcoma alone. The animal experiments have shown approximately the same ratio of all cancers to liver angiosarcoma, after background incidence is taken into account.

In calculating the probability per year of exposure that a highly-exposed worker will get angiosarcoma some time in his life, we found that the fraction of highly-exposed workers who have been currently diagnosed is 0.02; they have been exposed for an average of 17 years before diagnoses. The analysis, which required assumptions about the time distribution of man-years of exposure and the distribution of exposure durations preceding diagnosis, showed that only 38% of the highly-exposed workers who are expected to get angiosarcoma some time in their lives have been already diagnosed. Therefore the probability that one of these people will get angiosarcoma some time in their lives is $0.02/(17 \times 0.38) = 0.0031$ per year of exposure. In Appendix D the calculation is explained in greater detail.

The 17-year average concentration to which these workers were exposed was estimated to be 350 ppm on the basis of one study. Only one company has reported measurements of vinyl chloride for the jobs in their plant. These measurements, started in 1950, showed the highest exposure jobs ranged from 120 to 385 ppm before 1960, when the exposures were reduced because of suspected toxicological problems with vinyl chloride. In estimating the average, it was assumed that the other factories, most of which probably did not monitor the concentration of vinyl chloride, were less concerned about industrial hygeine and therefore took fewer pains to keep the levels low.

In predicting the human angiosarcoma rate from the animal dose-response data, it was projected, from the linear model, that exposure to vinyl chloride would cause 0.071 cases of liver angiosarcoma and

0.15 cases of all types of cancer per million people per year per ppb of continuous exposure. Details of these calculations are given in Appendix B. Converting to a 7-hour per day, 5 days per week work schedule of exposure to 350 ppm, the model predicts an incidence rate of 0.0052 per person-year exposure. It is shown in Appendix D that this rate is numerically indistinguishable from the rate of 0.0031 calculated from the human data, considering the known quantifiable errors of estimating the parameters of the animal and human data. It can be concluded that the slope of the linear animal dose-response relationship for angiosarcomas is consistent with the human data.

The extrapolation of the animal dose-response relationship to a concentration of 17 ppb (the average concentration around the uncontrolled plants) yields the following predicted number of cases in the 4.6 million people living within 5 miles of the plants. For details see Appendix B.

	Cases per year of exposure	
Type of effect	Linear model	Log-probit model
All cancer	11	0.1 - 1.0
Liver angiosarcoma	5.5	0.05 - 0.5

This is the expected number of cases projected to be caused per year at current levels of emissions; the people exposed now will not be diagnosed for another 15-20 years. Similarly, any cases observed now would have been caused 15-20 years ago (if they were in fact caused by vinyl chloride) when production was about 10% of current levels.

In order to arrive at a final estimate of the number of people adversely affected by vinyl chloride emissions, the important results of this analysis to consider are as follows: 1) the number of cancers at all sites caused by vinyl chloride is twice the number of liver angiosarcomas; 2) the number of people with severe liver damage is 30 times the number of liver angiosarcomas; 3) the animal model predicts that the number of liver angiosarcomas in the population around plants is 5.5 cases per year of exposure; 4) the number of cases calculated from the human data is 60% of the number predicted from the animal model; 5) the use of a log-probit model for extrapolation to low doses gives predictions of 0.1 to 0.01 times the number predicted by the linear model; 6) the error in the estimate of 5.5 cases per year ranges from + 55% to -10%. This error includes statistical uncertainty in estimating the dose-response, uncertainty in ambient concentration estimates, and errors resulting from not considering exposures beyond 5 miles or decomposition of vinyl chloride in the atmosphere. It is not symmetrical because it includes possible effects beyond 5 miles from the plants, which were not explicitly considered in the analysis. It does not account for our uncertainty about the appropriateness of using a

linear model extrapolated to zero dose; or of extrapolation from animal data; 7) the quantifiable error in the rate calculated from the human data is about + 67%. This includes uncertainties in the 17-year average dose received by the workers, uncertainty in the number of hours per day of actual high exposure, and uncertainty in the fraction of highly-exposed workers who have been diagnosed with liver angiosarcoma. Other errors can not be quantified, and are discussed in Appendix D.

When all these uncertainties are considered, our judgement is that the number of liver angiosarcoma cases produced per year of exposure in people residing near vinyl chloride plants is somewhere between less than one and 10 cases. The cases produced by this year's exposure will not be diagnosed until 15 to 20 years from now. If the EPA regulations are implemented, the number of cases is expected to be reduced in proportion to the reduction in the ambient annual average concentration, which is expected to be 5% of the present level.

The vinyl chloride exposure around plants is also producing somewhere between less than 1 and 10 cases of primary cancer at other sites, mainly lung, brain and bone. Assuming no threshold for liver damage somewhere between less than 1 and 300 cases of serious liver damage would be predicted. The number of liver damage cases is likely to be less than this because the assumption of no threshold is likely to be wrong.

In order to find out whether people living near VC-PVC plants have, as of 1974, had higher rates of liver angiosarcoma diagnosis than the overall U. S. population, a search of the residence records of all known liver angiosarcoma cases in the last 10 years was performed. Out of 176 cases where residence at time of death was known, 3 people lived within 5 miles of a plant. Unfortunately, the diagnosis of these cases has not yet been confirmed by the National Cancer Institute. In addition one infant whose parents lived within one mile of a plant died of a relatively common liver tumor. It was shown in Appendix E that this rate of occurrence is not higher than the national average. However, the survey is too incomplete to draw any conclusions at the current time.

Considering the results of the foregoing analysis, one would only now expect to be seeing some evidence of vinyl chloride exposure. If the highest rate in our range were actually occurring, 10 cases of liver angiosarcoma per year of exposure are being produced; 15-20 years ago when the vinyl chloride production 3as 10% of current levels, one case would be expected per year of exposure (with constant population). This is to be compared to a background rate of 0.6 cases per year that are occurring now.

The survey of liver angiosarcoma cases would probably detect the existence of 10 cases over the 10 year period. Since this was not observed we can conclude that the real incidence is not significantly greater than the predicted upper limit of 10 cases initiated per year

of exposure unless migration of people in and out of the regions around plants has been excessive. If the lower rates in the range of the above analysis were to be true, increased incidence of angiosarcoma would not be observable.

Appendix A. Population and Exposure Estimates

This appendix describes the approach taken in estimating the population at risk and the levels of exposure. The task is made easier by the use of a linear dose-response model to project health effects at very low exposures. This model implies that, for example, a given number of people exposed to emissions from two plants, each at the same distance from the people, would suffer the same number of health effects as twice as many people at the same distance from one plant.

More formally, with a linear dose-response relationship, the number of health effects is proportional to the sum, over all plants, distances, etc., of population times dose. This discussion shows how this quantity was estimated.

Population Estimates

The population estimates used in this analysis are all based on a study performed by the American Public Health Association under contract to the Office of Toxic Substances (APHA, Population Residing Near Plants Producing Vinyl Chloride, Aug. 1975, hereinafter cited as "APHA Study").

The APHA Study is based on the 1970 Census. For each PVC or VCM plant (or group of plants located close together), APHA determined the number of people residing within 0-1/2 mi, 1/2-1 mi, 1-3 mi and 3-5 mi. Further breakdowns by age and sex and by direction from the plant were also determined; however, as is discussed below, these detailed breakdowns were not used in this analysis.

For those plants located in Standard Metropolitan Statistical Areas (SMSAs), where Census Tract data is available, APHA asked a local respondent to allocate each tract to one of the distance ranges. Census tracts were not split. Independently, the Office of Planning and Evaluation, EPA, made a similar analysis for several selected plants in which Census tracts were split and one for which city block data was used. A comparison with the APHA data for those plants indicates that no significant errors were introduced by the APHA procedure. For untracted areas, population was assumed to be uniformly distributed over the area. For a more detailed description of the methodology used to estimate population, the reader is referred to the APHA report.

The total population residing at the indicated distances from PVC or VCM plants is shown in the following table:

Distance (mi)	Population
0-1/2	47,000
1/2-1	203,000
1-3	1,491,000
3-5	2,838,000
Total	4,579,000

Of course, some of these individuals are exposed to VC from more than one plant or are exposed to emissions from plants that are larger than average. These variations are taken into account in calculating exposure estimates, as described below.

There are several sources of error which result from the methodology used here. First, by estimating the exposed population from Census statistics on place of residence, we do not take into account the daily mobility of people, some of whom travel into areas of higher VC concentrations than their residences while others do the opposite. There does not seem to be any way of estimating the net effect of such travel or even whether it increases or decreases overall exposure, short of an analysis of commuting and travel patterns in the 42 communities included in this study. In general, it might be noted, however, these plants do not appear to be located in large central business districts to which large number of non-factory workers commute. Given the much greater uncertainties that are inherent in the estimation of dose-response relationships, it does not appear to be worth the effort to do such anaylses.

Second, the overall U.S. population has grown about 5% since the 1970 Census, but it is not known whether the areas covered in this study have grown similarly. The error here again seems small compared with other uncertainties.

Third, people living further than 5 mi from plants are not included. The effects of this error are considered below in the context of the overall calculation.

Fourth, even though information was available on the distribution of exposed populations by age, sex, and direction from the plant, this data was not used. The data on age and sex was not used because there is no information on how susceptibility to the effects of exposure to VC would vary with these factors. The data on distributionn of population by direction from the plants could have been used, together with data on the distribution of the ambient VC concentration by direction, to develop a more accurate estimate of the overall population exposure to VC. An examination of several communities with large exposed populations suggested, however, that the populations were either distributed in many directions or did not appear to be correlated with the angular distribution of VC concentration. Since the more detailed analysis would require 16 times as much calculation, it was judged not be worth the effort, particularly given the much greater uncertainties in other parts of the analysis.

Ambient Concentration Estimates

It was decided early that the measure of exposure to be used is the long-term (annual) average ambient concentration. At one level, this assumption is a consequence of the linear (single shot) dose-response relationship. But regardless of the specific form ot the dose-response relationship, it appears reasonable to assume that the probability that

any given individual suffers an adverse health effect would depend on the long-term integrated exposure of the individual, independently of the functional relationship between the probability and the exposure level. Indpendent of the actual truth of this assumption, however, is the absence of any data on responses to peak exposures, either from the occupational experience or animal experiments. Thus, there is no alternative to this assumption if a quantitative projection of effects is to be made.

The estimates of average annual concentrations were derived from diffusion modeling, using standard techniques. Two independent modeling efforts were made. The first was performed by the Monitoring and Data Analysis Division of EPA's Office of Air Quality Planning and Standards in Research Triangle Park, N. C. This analysis took one representative set of meteorological conditions and devoted considerable effort to investigating the effects of different plant source configurations for controlled and uncontrolled PVC and VCM plants. In general, for average annual concentrations, the results for uncontrolled PVC plants were quite similar for the plant configurations analyzed, as were those for uncontrolled VCM plants (although, of course, emissions from PVC plants are very different than those from VCM plants). The results for typical PVC and VCM plants are shown in Figs. A-1 through A-4.

The second independent effort was performed by Teknekron, Inc. under the contract with EPA's Office of Planning and Evaluation. In this analysis, plant configurations were fixed (except for size and the difference in pattern of emissions between PVC and VCM plants), but an effort was made to estimate the distribution of meteorological conditions and, to some extent, topography for each site.

The results of the two sets of calculations were extremely close. The following table shows the average annual concentration of VC emitted from a typical PVC plant as a function of distance (that is, averaged radially through all directions), as determined by the two studies.

	Vinyl Chloride Concentration (ppb)	
Distance (mi)	OAQPS	Teknekron
0.25	301	323
0.75	76	57
1.00	--	37
1.50	26	--
2.00	--	15
3.00	10	8
4.00	--	5.7
4.50	5.6	--
5.00	--	4.0

A dash (--) in the table indicates that a value was not determined for precisely that range. The results appear generally to be within 25% of each other, with the OAQPS results lower than the Teknekron results at very close ranges and higher at longer ranges.

In general, the closeness of the two sets of independent results serves as a confirmation of both. Of course, since both use similar methodologies, it is possible that they share some of the same errors. It has not proved possible to compare these modeling results with actual monitoring data in a systematic way, and this is an important shortcoming of the analysis as it stands at present. Summaries of the ambient measurements have been examined, however, and they appear to be generally consistent with the modeling results.

For the actual calculations, it was decided to use the Teknekron results, since these showed how ambient concentrations would vary with meteorological conditions (although, in retrospect, it turned out that these variations made little difference in the final result). The sites listed in the Teknekron report divided naturally into four categories, which we designate as Low (L), Average (A), High (H), and Very High (VH), based on the ambient concentration projected to result from the same level of emissions. (Variation among sites due to the number and size of the plants are factored into the analysis separately and are discussed below). Table A-1 shows the category to which each location is assigned. The relative ambient concentrations for the four categories are:

Low	0.56
Average	1.00
High	1.55
Very High	2.55

OAQPS provided information which categorized each plant by size as "Average" or "Large." The typical "Average" VCM plant had a production of 700 million lb/yr, and the typical "Large" VCM plant 1300 million lb/yr. For PVC plants, the typical "Average" plant used 150 million lb/yr and the typical "Large" plant 350 million lb/yr. It was assumed that large plants would have proportionately greater emissions. It is estimated that uncontrolled PVC plants emit about 4% of the vinyl chloride processed and VCM plants, about 0.3%. Table A-1 also shows, for each location, the number and size categories of plants located there. The letter "L" indicates a "Large" plant; thus, for example, the designation "2" means two "Average" plants and "2 & 2L" means two "Average" and two "Large" plants.

Overall Exposure Estimates

Table A-1 also shows the populations residing at the indicated distances from individual plants. To determine the equivalent exposure (compared to exposure from a single average size plant at a location with average meteorological conditions), each of the population figures must be multiplied by two factors, one reflecting meteorological conditions at that location and one reflecting the number and size of plants at the location. Thus, for example, in Texas City, Texas, each individual is exposed to emissions from two average size plants and one large plant (equivalent to 2.3 average plants) but under "Low" meteorological conditions (leading to 0.56 of the concentration that would be expected under average conditions). Thus, these individuals are exposed to the equivalent of 0.56 x 4.3 = 2.4 average plants' emissions under average

conditions. Similar calculations were performed for each location in Table A-1 and the results summed to obtain the values shown as "Weighted total population" in Table A-2.

The weighted total population figures are then multiplied by the average annual concentration of vinyl chloride, as derived from the diffusion modeling. The sum of these figures is the total population exposure. These results are shown in Table A-2. The total exposure is estimated to be 76.4 million people x ppb. Thus, the total exposure of the U.S. population to vinyl chloride due to emissions from these plants is equivvalent to 76.4 million people exposed to 1 ppb, or 7.64 million people exposed to 10 ppb, etc. Probably the simplest way to understand this figure is in terms of the average exposure of those who are exposed. Since there are a total of 4.6 million people exposed within 5 mi of plants, the average exposure of these people is 76.4/4.6 or 17 ppb.

We can also use these figures to gain some insight into the distribution of the aggregate exposure (and hence of the resulting adverse health effects). We can see from Table A-2 that only about 3% of the exposure is a result of emissions from VCM plans, with the remaining 97% coming from PVC plants. It also appears that the bulk of the health effects will be occurring from 1 to 5 miles from the plants, rather than within one mile, since much larger numbers of people live at the greater distances.

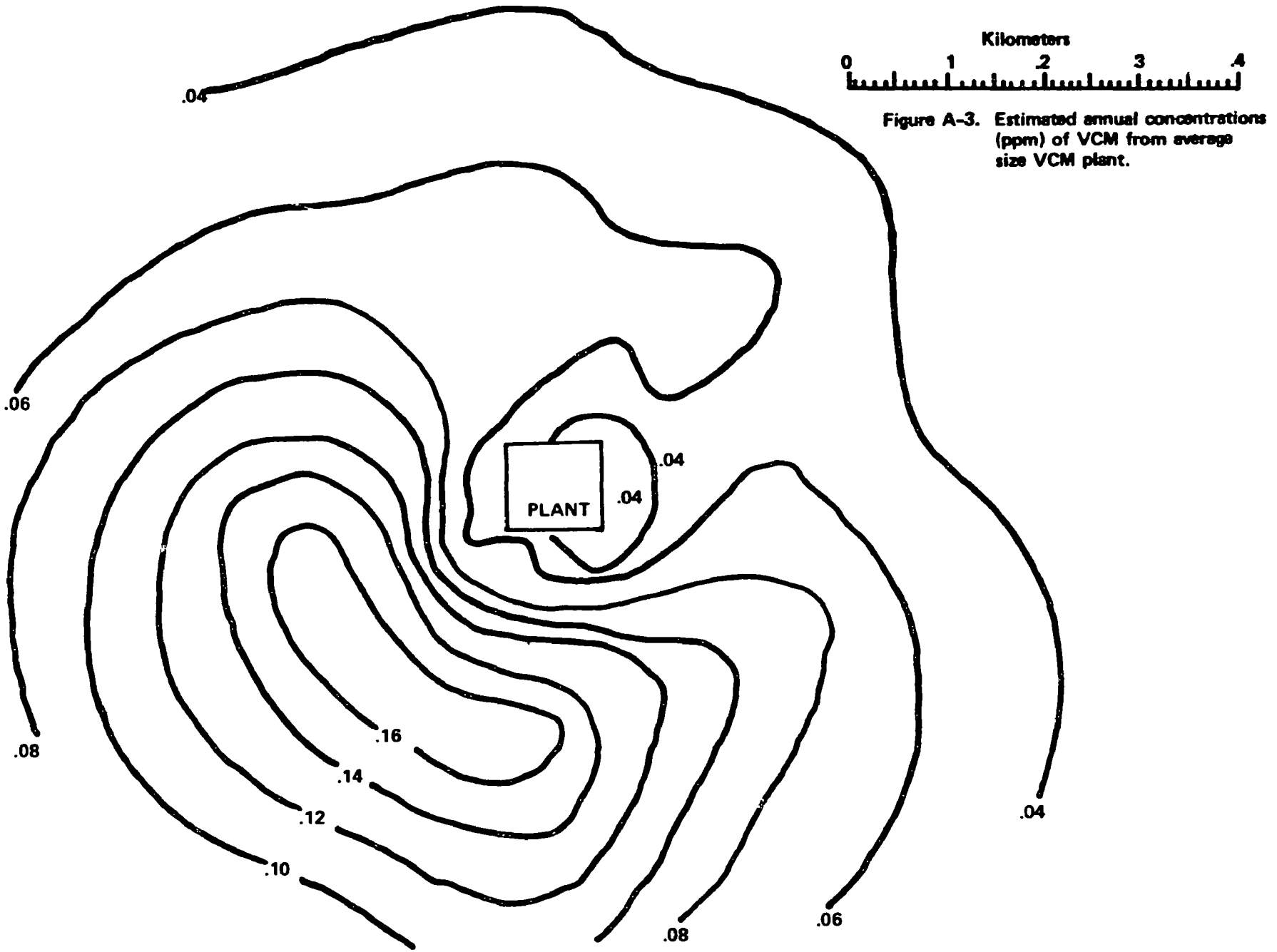


Figure A-3. Estimated annual concentrations (ppm) of VCM from average size VCM plant.

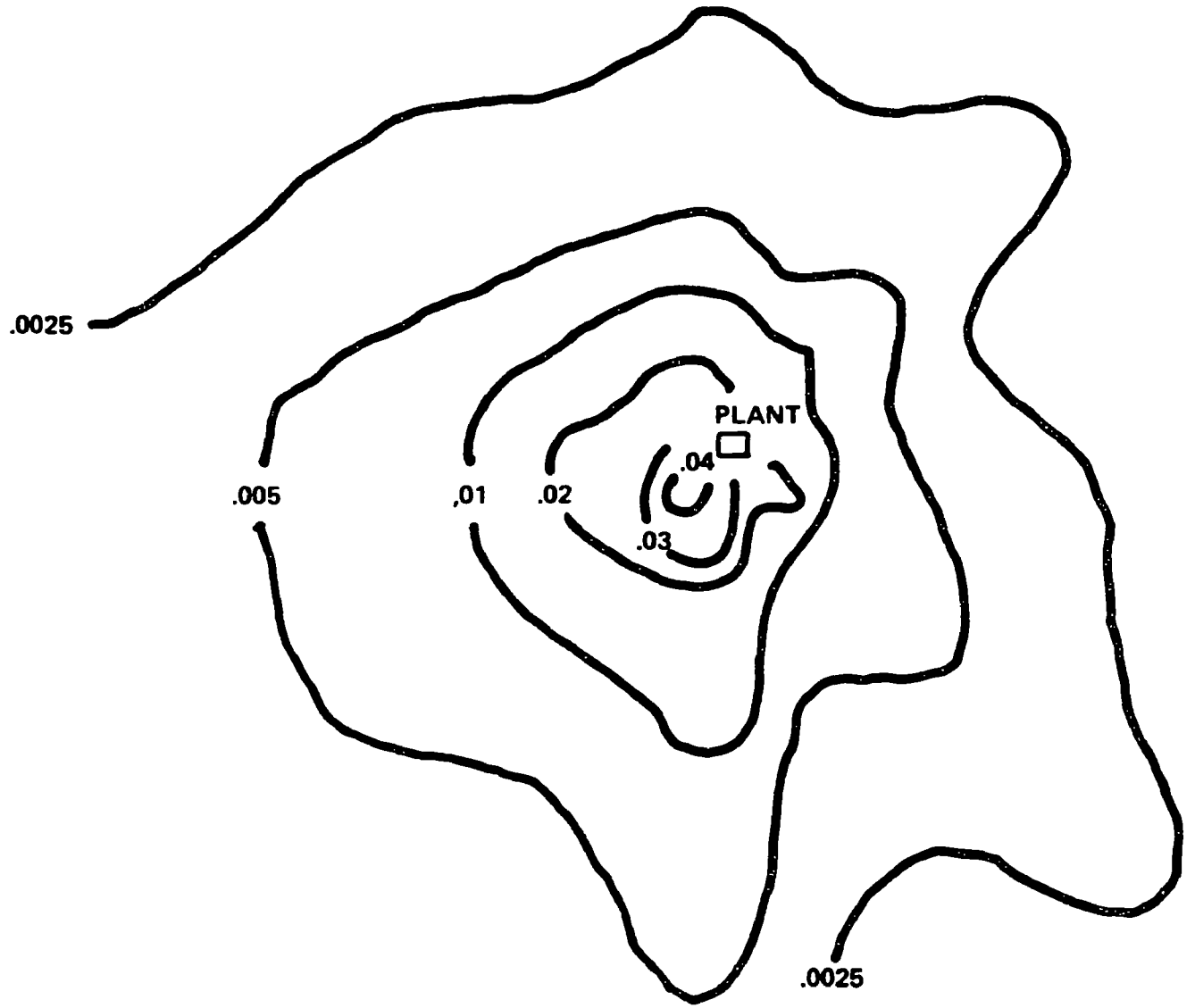


Figure A-4. Estimated annual concentrations (ppm) of VCM from average size VCM plant.

TABLE A-1 Population Exposed by Location

Location	No. & Size of Plants	Meteorological Conditions	Population vs. Distance (mi) 0-1/2	1/2-1	1-3	3-5
(a) PVC Plants						
Carson City, CA	2	A	--	16,541	259,309	405,461
Saugus, CA	1	H	--	10,935	--	12,029
Delaware City, DE	1&1L	A	--	--	6,970	9,218
Pace, FL	1	A	--	--	--	7,071
Henry, IL	1L	A	37	146	1,161	2,013
Illiopolis, IL	1	L	30	117	922	1,597
Calvert City, KY	1	A	102	398	3,134	5,436
Louisville, KY	1L	A		6,315	111,146	146,000
Plaquemine, LA	1	A	177	673	5,328	9,237
Baton Rouge, LA	1	A	--	--	25,615	54,193
Perryville, MD	1L	H	--	2,091	11,091	9,791
Fitchburg, MA	3	A		34,395	67,767	114,489
Springfield, MA	1	A		8,258	40,671	108,966
Midland, MI	1	L	492	1,899	15,045	26,067
Aberdeen, MS	1L	VH	114	442	3,504	6,073
Burlington, NJ	2	L		8,159	122,419	230,361
Pedrickton, NJ	1	A	--	--	9,113	98,992
Passaic, NJ	1	L	22,512	29,458	194,601	269,259
Kearny, NJ	1	L		18,656	214,594	696,928
Flemington, NJ	1	A	81	306	2,394	4,153
Hicksville, NY	1	L	5,900	20,702	143,760	215,230
Williamsville, NY	1	L	11,522	12,552	51,872	113,422
Ashtabula, OH	1	A	434	1,671	13,239	22,937
Huron, OH	1	L	98	380	2,988	5,175
Avon Lake, OH	1L	L	827	5,511	16,398	8,022
Painesville, OH	1&1L	A	--	--	21,550	16,434
Oklahoma City, OK	1L	L	--	--	25,526	73,581
Pottstown, PA	1L	H	--	2,447	36,121	30,382
Deer Park, TX	1L	H	--	12,820	32,151	86,508
Freeport, TX	1&1L	L	--	--	4,746	15,879
Texas City, TX	2&1L	L	3,440	--	19,460	34,751
Pt. Pleasant, WV	1	H	263	1,007	7,984	13,836
S. Charleston, WV	1	VH		5,698	40,685	53,432
(b) VCM Plants						
Geismar, LA	3	A	62	233	1,852	3,211
Baton Rouge, LA	1	A	--	--	25,615	54,193
Lake Charles, LA	2	A	--	--	11,601	44,100
Plaquemine, LA	1	A	177	673	5,328	9,237
Norco, LA	2	A	215	823	6,525	11,306
Deer Park, TX	2	H		12,820	32,151	86,508
Freeport, TX	1	L	--	--	4,746	15,879
Calvert City, KY	1L	A	102	398	3,134	5,436
Guayamilla, PR	1	A	202	780	6,173	10,692

FOOTNOTES:

a/ Numbers followed by "L" indicate "Large" plants as defined in the text. Other numbers indicate "Average" size plants.

b/ Ratio of ambient concentration to emissions is characterized as Low (L), Average (A), High (H), or Very High (VH).

c/ Adjusted to show effect of multiple exposures at varying distances from plants. Not to be multiplied by number of plants.

TABLE A-2 Aggregate VC Exposure

	Distance From Plant (mi)				
	0-1/2	1/2-1	1-3	3-5	Total
(a) PVC Plants					
Weighted total population	34,000	228,000	2,013,000	3,439,000	
VC concentration (ppb)	323	57	15	5.7	
Total exposure (million population x ppb)	11.0	13.0	30.2	19.6	73.8
(b) VCM Plants					
Weighted total population	1,200	37,000	169,000	434,000	
VC concentration (ppb)	113	20	5.2	2.0	
Total exposure (million population x ppb)	0.1	0.7	0.9	0.9	2.6
Total for all plants					76.4

Appendix B. Estimates of Effect Rates from Animal Data

In analyzing the effects of vinyl chloride, we are fortunate to have at least semi-quantitative data for both human and animal exposures. Choices had to be made concerning how to use this data. Vinyl chloride is known to cause both cancer and non-cancer effects in humans. With respect to cancer effects, we have animal experiments in which rats were exposed to known concentrations for known periods of time. We also have the human occupational experience, in which increased incidence of liver angiosarcomas and other cancers were observed in exposed workers. Ideally, we should use human data throughout and avoid the problem of extrapolating from an animal model to human beings. Unfortunately, we do not have good data on the level of exposure of workers. In arriving at a specific number to write down and use in the calculations, it would be necessary to guess at these factors. We decided, therefore, to derive a dose-response relationship from the animal data, for cancer effects, but to use the human data to the greatest extent possible to confirm or deny the validity of the relationship. These checks are described in Appendix D. Since both the human and the animal data involve exposure at high levels, the difficulty in extrapolation from high to low exposure levels would be the same in either case.

With respect to effects other than cancer, the animal data is too fragmentary to estimate quantitatively the ratio between cancer and non-cancer effects caused by exposure to vinyl chloride. However, the human data does permit an estimate of this ratio, and this estimate can then be used together with the dose-response estimate for cancer to place some limits on the magnitude of the non-cancer effects.

The Animal Data on Cancer

The basic experiment is Maltoni's experiment BT1. Sprague-Dawley rats were exposed by inhalation to a specified concentration of vinyl chloride for 4 hr/day, 5 days/week for 52 weeks. After the 52 weeks, the animals were not exposed to vinyl chloride but were observed for the remainder of their lifetimes. The results of the experiment were as follows:

VC Concentration (ppm)	Liver Angiosarcomas	All Tumors
10,000	9/61 (15%)	38/61 (62%)
6,000	13/60 (22%)	31/60 (52%)
2,500	13/59 (22%)	32/59 (54%)
500	7/59 (12%)	22/59 (37%)
250	4/59 (7%)	16/59 (27%)
50	1/59 (2%)	10/59 (17%)
0	0/58 (0%)	6/58 (10%)

Two conclusions can be drawn immediately from these results. First, the rate of occurrence of both liver angiosarcomas and total cancers increases much more slowly with dose above 500 ppm than below this concentration. The cause of this phenomenon is not understood, but, whatever it may be, it does not appear to be relevant to extrapolation to lower doses in the parts-per-billion range. Hence, all the curve-fitting reported here is done only for the data for 500 ppm and below.

Second, the control group had no liver angiosarcomas, but about 10% of them did have other types of cancers, as is to be expected. Therefore, in estimating the dose-response relationship for total cancers, it will be necessary to use a method which allows for a positive response at zero dose.

Extrapolation to Low Doses

It is widely understood in the scientific community that no firm logical basis can exist for extrapolating data to levels many orders of magnitude beyond the range of experimental observation. In spite of this, two alternative assumptions are frequently made in the literature. The first of these is that the response is linear in dose, e.g., half as many effects are produced at half the dose. This is also referred to as the "one-hit" model, since it would follow logically from the assumption that each minute increment of exposure to a carcinogen has the same independent probability of causing a cancer regardless of the dose level. This assumption is generally accepted as prudent in radiation carcinogenesis. For carcinogenesis in general, this model is usually considered to provide an upper limit to the level of effects likely at extremely low doses, because the possible existence of detoxification mechanisms might render small doses ineffective in contributing to cancer effects and thus result in a threshold below which no effects would occur. The second assumption frequently made is that the response is linear when the logarithm of the dose is plotted against the proportion of responses expressed in a probit scale (i.e., the value of the argument of the cumulative normalized Gaussian distribution function corresponding to that proportion); for convenience, we refer to this as the "log-probit" model. This model is derived from the assumption that individuals in the population have a statistical distribution of susceptibility to cancer effects which is normally distributed with log dose.

The linear model is much easier to apply, since the number of effects depend only on the number of individuals exposed and their average dose. The log-probit model, on the other hand, requires data as to the distribution of doses in the population and is therefore more likely to be influenced by anomalies in the methods for estimating population exposure. For this reason and because of the conservativeness of the linear model, the calculations were made using the linear model, but a sensitivity analysis was performed to show how the results would vary were the log-probit model used.

Straight lines were fitted to Maltoni's data using a maximum-likelihood method. Essentially, this method assumes that the probabilities of cancer at the different doses were related by a linear function and detemines the values of the slope and intercept that would make the likelihood of the observed results as high as possible. Mathematical details are provided in Appendix C.

For the data on liver angiosarcoma, the line was constrained to go through the origin. (Without this constraint, a slightly negative intercept was obtained.) With the constraint, the following relationship is obtained:

$$P = 2.53 \times 10^{-4} d$$

where P is the probability of a liver angiosarcoma and d is the dose in ppm. For all tumors, the corresponding line is

$$P = 0.123 + 5.26 \times 10^{-4} d$$

Here, the intercept is the best estimate from all data at 500 ppm and below of the cancer rate in the absence of vinyl chloride; the slope is the best estimate of the rate at which tumors are caused by exposure to vinyl chloride. Thus, inn the animals, vinyl chloride appears to cause about one other cancer for each liver angiosarcoma. Estimates of the total number of cancers caused by vinyl chloride are based on the slope of this line, not on the intercept.

The standard deviations of the estimates of the slope were found to be 6.9×10^{-5} for liver angiosarcoma and 1.1×10^{-4} for all tumors. (These estimates are derived from large-sample theory). It cannot be emphasized too much that the standard deviations reflect only that uncertainty in the estimates that is due to limited sample size; they are derived from the linear model and cannot reflect the much greater uncertainty due to our ignorance of whether the linear model is correct. They also do not reflect the effects of the part-time exposure used in the experiments or, most importantly, of the difference between human beings and Sprague-Dawley rats; these are discussed below.

The goodness of fit is shown in the following table, which compares the actual data obtained in the experiments with the values expected from the above equations.

	Liver Angiosarcoma		All Tumors	
Dose (ppm)	Actual	Expected	Actual	Expected
0	0	0.00	6	7.16
50	1	0.75	10	8.84
250	4	3.74	16	15.05
500	7	7.47	22	22.81

In order to test the sensitivity of these projections to the assumed linear form of the dose-response relationship, the data for liver angiosarcoma was also fitted to a log-probit equation. Using an unweighted

least-squares fit to the data for doses of 500 ppm or less, the following equation is obtained:

$$\text{probit} = -3.71 + 0.932 \log \text{dose}$$

where log indicates common (base 10) logarithm and dose is in ppm. The fit is extremely close: the maximum difference between predicted and actual values is 0.02 probits.

Both the linear and log-probit fitted curves are plotted in Fig. B-1 on a log-probit scale. It can be seen from this graph that, in the range of concentrations of interest (say, 5 to 300 ppb), the log-probit projection yields risks of one to three orders of magnitude lower than the linear projection. Since the result of a complete log-probit analysis of human effects due to exposure to vinyl chloride in the ambient air near plants would tend to be dominated by the high concentrations close to the plants (unlike the linear analysis), the log-probit analysis would yield final results one to two orders of magnitude lower than the linear model.

Extrapolation to Human Exposure

The equations derived above can be used to project what the response of rats would be in similar experiments at much lower doses. To apply these results to human community exposures, it is necessary to modify the results to reflect 24-hour exposure and, most importantly, the difference between humans and rats. The latter is particularly problematical. The remainder of this Appendix will be based on animal data. Human data will be discussed in Appendix D.

In the experiments, the animals were exposed to vinyl chloride for 4 hr/day, 5 days/week. In the community, the exposure would be continual for 24 hr/day, 7 days/week. This effect can be corrected for by dividing the continuous dose received by people by (7x24)/(5x4) = 8.4 and using the same linear dose-response function to calculate the risk. This is mathematically equivalent to multiplying the slope by the same amount.

Adjusting for the difference between humans and rats is much more difficult. As in the extrapolation to low doses, very little evidence is available. Furthermore, controlled experiments involving human carcinogenesis are unlikely to be carried out. In spite of the lack of evidence, the consensus of the scientific community appears to be that, if an assumption must be made, it should be assumed that the same number of cancers would be induced in humans over their lifetimes as are induced in rats over their lifetimes. With this assumption, the one-year exposure of the experimental is expected to cause the same probability of cancer (i.e., the same incidence rate) as about 30 years of exposure to humans at the same concentration. Thus, to determine the annual rates of cancer induction in humans,

the rates derived above should be divided by 30.

Making these adjustments and also converting the units to cases per million population per ppb per year, we obtain a rate of 0.071 liver angiosarcomas and 0.147 total cancers (in excess of background rates) per million population per ppb vinyl chloride per year. The standard deviations of the estimates, which, again, reflect only the statistical uncertainty due to limited sample sizes, are 0.019 and 0.031, respectively.

Incidence of Non-cancer Effects

Liver damage has been a frequent observation in animals exposed to vinyl chloride. The lowest dose in chronic experiments (times longer than 3 months) at which non-cancerous liver effects are observed is 100 ppm (Torkelson, et al., 1961). The effect observed was liver enlargement which cannot be called damage since the microscopic structure was normal, but it is an indication that the liver is affected in some way by vinyl chloride. Of all reports on animals the lowest dose causing liver cellular degeneration is 500 ppm (7 hrs/day, 5 days/week, for 4-5 months). A Russian report of bone resorption, cardiovascular impairment and neurological changes in the hypothalmus of rats and rabbits at concentrations of 12-16 ppm for 6 months (Basalaev, 1972) has also appeared. It is unfortunate that we currently have no published reports of pre-cancerous liver damage occurring in the same experimental group of animals in which cancer later develops. Therefore there is no way to estimate the incidence ratio of non-cancer to liver angiosarcoma effects in animals.

The human data on non-cancer effects is discussed in Appendix D.

Overall Effect Rates

In Appendix A, it was estimated that the 4.6 million people living within 5 mi of PVC or VCM plants would be exposed, on the average, to 17 ppb of vinyl chloride. Combining this information with the dose-response estimates derived above, we can calculate that, for example, vinyl chloride emisssions in the absence of control would cause 4.6 x 17 x 0.071 = 5.5 cases of liver angiosarcoma per year in the U.S., using the linear model. Similar calculations for all cancer yield the following results:

Type of Effect	Cases Caused per Year
Cancer	
Liver angiosarcoma	5 1/2
All cancer	11

It should be realized that cancers caused by vinyl chloride have about a 20-year latent period. Thus, we would not expect to observe these numbers of cancers occurring now; rather, these are the numbers

that are estimated to be initiated now but which will produce symptoms perhaps 20 years from now if emissions remain unchanged from current uncontrolled levels. Similarly, we would expect that cancers caused by vinyl chloride that are showing symptoms now would have been caused by emissions over the past 20 years, during which total vinyl chloride production increased from about 10% of its current leveel.

Error Analysis

The following discussion attempts to estimate the errors involved in this analysis other than the errors introduced by extrapolation from high to low doses and from animals to man, which are discussed in Appendix D. Quantitative estimates are provided below for the following sources of error:

(1) Errors in the slopes of the dose-response lines due to the limited sample sizes in the experiments.

(2) Errors in estimating the ambient concentrations around plants.

(3) Errors resulting from not considering effects on the population living further than 5 mi from plants.

(4) Errors resulting from not considering the decomposition of vinyl chloride in the atmosphere.

The standard deviations of the estimates for the slopes of the dose-response lines were calculated from maximum-likelihood large-sample theory, as described in Appendix C. As mentioned above, the results are 27% and 21% of the estimated slopes for liver angiosarcoma and all cancer, respectively.

Ideally, an estimate of the errors in the diffusion modeling could be derived from a comparison with actual monitoring data. Unfortunately, such a comparison is not available. In its absence, we use the difference between the two independent estimates as a measure of the degree of uncertainty in the estimates. As was noted in Appendix A, the two sets of results were generally within 25% of each other.

We can estimate the magnitude of the errors due to the 5-mile cut-off and vinyl chloride decomposition as follows. Suppose that, say, 10 million people live between 5 and 10 mi from the plants where they would be exposed to an average concentration of VC of about 2.4 ppb, based solely on the diffusion modeling. (The figure of 10 million people is chosen to show the sensitivity of the calculation to the 5-mile cut-off. The 5-10 mile annulus contains 3 times the area of the 5-mile circle, but would probably contain less than 3 times the population, since in many cases the bulk of the urban area would be within the 5 mi distance.) This exposure would cause 3.5 cases of cancer of all types per year and corresponding numbers of other health effects, according to the linear model. However, vinyl chloride is believed to decompose in the

atmosphere with a half-life estimated at about 6 hours. Assuming an overall average wind speed of 10 mi/hr, the average concentration in the 5 to 10 mile annulus would be reduced by decomposition by about 8%, so about 3.2 cases of cancer would be occurring there. At the same time, decomposition would reduce the average concentration within 5 miles as well, by about 3.4%. The overall effect of these compensating errors would be to increase the estimate by about 25%.

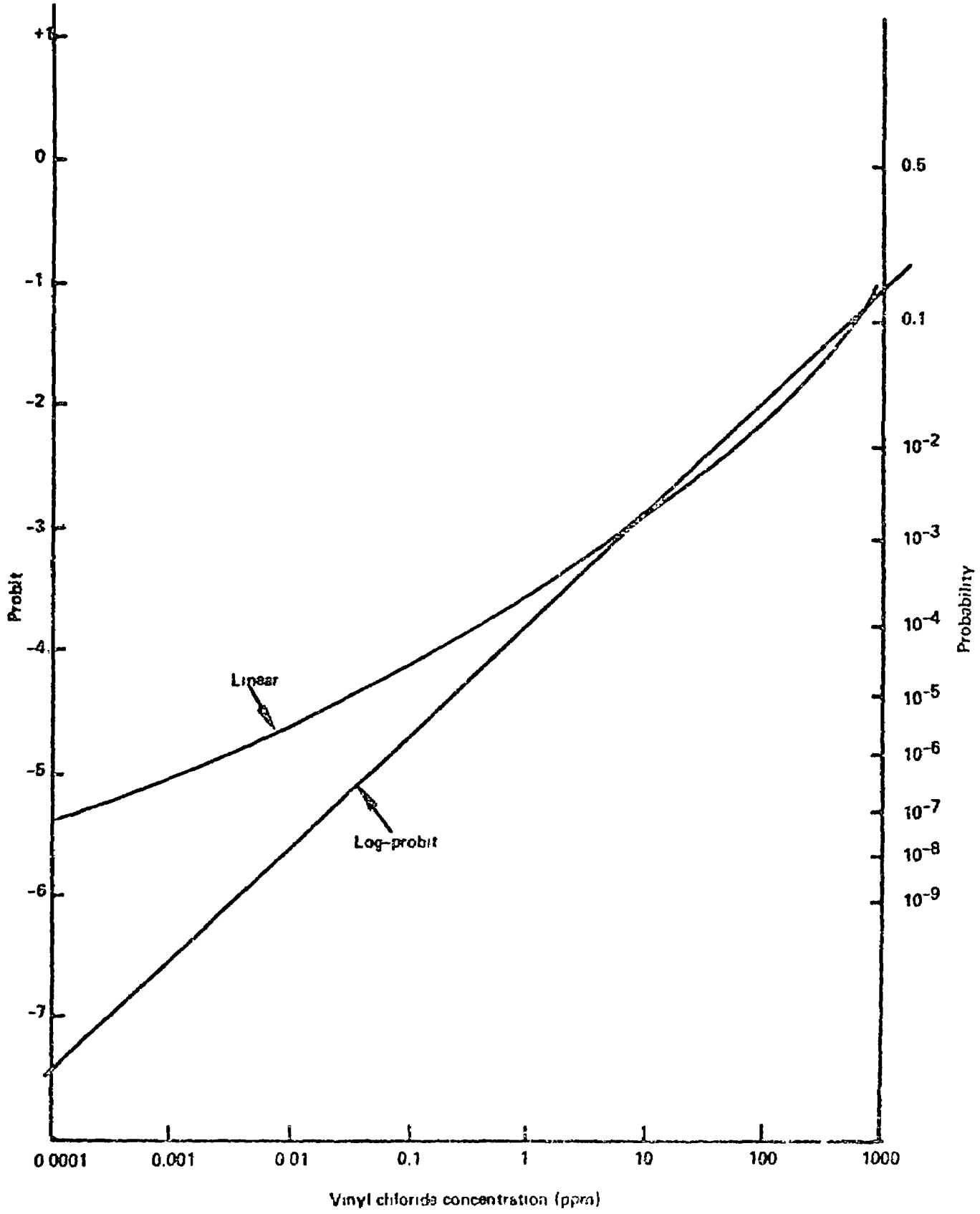
Assuming that the first two sources of error are independent, the estimates can be combined using a Pythagorean formula. Thus, the combined error estimate would be the square root of

$$(.21)^2 + (.25)^2$$

or about 33% of the estimated 11 cases of cancer per year predicted by the linear model. This is about 3.6 cases per year. Since the second two sources of error listed above are estimated to lead to an underestimate by about 2.8 cases per year, a total error estimate might be plus about 6 or minus about 1 cases out of 11 per year.

(Note: under the log-probit model, the effect of the 5-mi cut-off would be negligible.)

Figure B-1. Comparison of linear and log-probit projections for liver angio sarcoma (Maltoni experiment BT 1)



Appendix C. Mathematical Treatment of Dose-Response Data

The dose-response curves given in Appendix B were derived from the animal experiments using an extension of the standard maximum-likelihood (ML) method of statistical estimation. The results at different doses are combined and the line chosen is the one for which the likelihood of the observed results is the greatest. A discussion of the standard ML method may be found in any elementary text on mathematical statistics.

Equations for ML Estimators

Assume that M experiments (including the controls, if any) are performed. In the i-th experiment, n_i animals are exposed to a dose d_i and x_i responses are observed. We assume that the response of each animal is independent of the others, so each experiment is a set of Bernouilli trials in which the probability of response p_i is a function of d_i with unknown parameters. In particular, we consider two functional forms here:

$$p_i = \beta d_i \tag{1}$$

$$p_i = \alpha + \beta d_i \tag{2}$$

The method is readily adapted to other functional forms.

Eq. (1) will be called the "no zero response" case and is appropriate when there is no measurable response at zero dose. Eq. (2) will be called the "positive zero response" case and is appropriate when a measurable response occurs at zero dose. (The mathematics allows $\alpha < 0$, of course, which would imply at threshold below which no response would occur. Inferring the existence of a threshold is fraught with difficulty.)

For the positive-zero-response case, the joint probability of the results obtained is

$$L(\{x_i\}, \alpha, \beta) = \prod \binom{n_i}{x_i} (\alpha + \beta d_i)^{x_i} (1 - \alpha - \beta d_i)^{n_i - x_i} \tag{3}$$

(all sums and products are assumed to be over the range $i = 1, \ldots, M$ unless otherwise indicated). The values of α and β which maximize L (unless they fall on the boundary or $0 \le \alpha + \beta d_i \le 1$ for some i) satisfy the equations

$$\frac{\partial}{\partial \alpha} \log L = 0 \tag{4}$$

$$\frac{\partial}{\partial \beta} \log L = 0 \tag{5}$$

After simplification, Eqs. (4) and (5) reduce to

$$\sum \frac{x_i - (\alpha + \beta d_i) n_i}{(\alpha + \beta d_i)(1 - \alpha - \beta d_i)} = 0 \qquad (6)$$

$$\sum \frac{x_i d_i - (\alpha + \beta d_i) n_i d_i}{(\alpha + \beta d_i)(1 - \alpha - \beta d_i)} = 0 \qquad (7)$$

There are a set of two simultaneous 2M-th order algebraic equations for which no closed-form solution is possible. However, a numerical solution can be obtained by, for example, Newton's method for two variables which is described below.

For the no-zero-response case, Eq. (5) applies and is equivalent to Eq. (7) with $\alpha = 0$. This simplifies to

$$\sum \frac{x_i - n_i d_i \beta}{1 - \beta d_i} = 0 \qquad (8)$$

This is, again, a 2M-th order algebraic equation which can be solved numerically by the standard Newton's method, described below.

Asymptotic Variances

With the ML method, asymptotic variances of the ML estimators are readily obtained. (See S. S. Wilks, Mathematical Statistics (Wiley, 1962), pp. 379-81.) These are given by

$$\frac{1}{\sigma_\alpha^2} = E\left\{\left[\frac{\partial}{\partial \alpha} \log L\right]^2\right\} \qquad (9)$$

$$\frac{1}{\sigma_\beta^2} = E\left\{\left[\frac{\partial}{\partial \beta} \log L\right]^2\right\} \qquad (10)$$

for the positive-zero-response case. Eqs. (9) and (10) reduce to

$$\frac{1}{\sigma_\alpha^2} = \sum \frac{n_i}{(\alpha + \beta d_i)(1 - \alpha - \beta d_i)} \qquad (11)$$

$$\frac{1}{\sigma_\beta^2} = \sum \frac{n_i d_i^2}{(\alpha + \beta d_i)(1 - \alpha - \beta d_i)} \qquad (12)$$

Again, for the no-zero-response case, the corresponding result is obtained by setting $\alpha = 0$ in Eq. (12), which gives

$$\frac{1}{T_\beta^2} = \sum \frac{n_i d_i}{\beta^2 (1 - \beta d_i)} \tag{13}$$

Eqs. (12) and (13) were used in Appendix B to calculate the standard deviations of the slopes of the dose-response lines.

Newton's Method for One Variable

We wish to solve the equation $f(x) = 0$, where f has a continuous first derivative. Starting with an initial estimate x_0, we approximate the curve $y = f(x)$ by its tangent at $x = x_0$; the point where the tangent intersects the x - axis is an improved estimate of the root.

The equation of the tangent is

$$y - f(x_0) = f'(x_0)(x - x_0) \tag{14}$$

Setting $y = 0$ in Eq. (14) yields

$$x = x_0 - \frac{f(x_0)}{f'(x_0)} \tag{15}$$

Eq. (15) can be iterated until sufficient accuracy is obtained.

Newton's Method for Two Variables

Here, we wish to solve the equations

$$\begin{aligned} f(x, y) &= 0 \\ g(x, y) &= 0 \end{aligned} \tag{16}$$

and have an initial estimate x_0, y_0. The plane tangent to $f(x, y) - z = 0$ at $(x_0, y_0, f(x_0, y_0))$ is

$$(f_x, f_y, -1) \cdot (x - x_0, y - y_0, z - f) = 0 \tag{17}$$

or

$$(x - x_0) f_x + (y - y_0) f_y - (z - f) = 0 \tag{18}$$

where the subscripts indicate differentiation and all functions are evaluated at (x_0, y_0). Similarly, the plane tangent to $g(x, y) - z = 0$ at $(x_0, y_0, g(x_0, y_0))$ is

$$(x - x_0) g_x + (y - y_0) g_y - (z - f) = 0 \tag{19}$$

The planes given by Eqs. (18) and (19) intersect in a line, which in turn intersects z = 0 in a point which is an improved estimate of the root. This point can be obtained by solving Eqs (18) and (19) simultaneously with z = 0. This gives

$$x - x_0 = - \frac{f y_y - g f_y}{f_x g_y - f_y g_x} \tag{20}$$

$$y - y_0 = - \frac{f_x g - g_x f}{f_x g_y - f_y g_x} \tag{21}$$

Eqs. (20) and (21) can be iterated until sufficient accuracy is obtained.

APPENDIX D: USE OF HUMAN DATA TO ESTIMATE RISKS

In Appendix B the linear model describing the dose-response curve for the incidence of liver angiosarcoma in rats was modified by two factors in order to estimate the number of cases of human angiosarcoma in human populations. These two (multiplicative) factors were 8.4, to convert the 4 hrs/days, 5 days/week rat exposures to continuous exposures, and 1/30 = 0.033, to convert the annual rates in rats to in humans. In this appendix the available human data on liver angiosarcoma were examined to validate these factors, revised estimates of the number of human cases per year of exposure to ambient vinyl chloride concentrations around plants are made, and the number of people incurring effects other than liver angiosarcoma is estimated. The emphasis is placed on the quantitative comparison of data in rats and humans.

Interspecies Comparison of Life Expectancy and Angiosarcoma Latent Times

The most obvious difference between rats and people is their relative size and attendant metabolic rate and life expectancy. Both life expectancy and the time required for tumors to develop are independent manifestations of the basic differences in metabolic rates.

According to the 1970 U.S. census data, the life expectancy of one-year old infants in the U.S. is 75.6 years for females and 68.3 years for males. This is to be compared to about 100 weeks or 1.93 years for rats. The ratio of life expectancies is therefore about 1.9/72 = 0.026.

The time required for tumor development in people can be estimated from the case histories of 14 confirmed cases of liver angiosarcoma, all of whom are highly-exposed workers in the vinyl chloride industry (reference 2). The average time between first exposure to vinyl chloride and diagnosis is 19.6 years, and the average duration of exposure is 17.2 years. The distribution of exposure durations preceding diagnosis among these cases is approximately log normal, i.e. it is a normal distribution when plotted against the logarithm of latent time. The median time is 17 years, and the variance is 0.15 units of log (time) per one standard deviation. By contrast, Maltoni found that the average time in rats between onset of exposure and appearance of tumors was 80 weeks (after a 52-week exposure), regardless of dose between 10,000 ppm and 250 ppm. The one liver angiosarcoma which appeared in the 50 ppm group occurred 135 weeks after onset of exposure, but this one case is regarded as insufficient information to disprove the conclusion that the latent time in rats is independent of dose. The approximate ratio of times required for tumor development in humans and rats is 1.54/19.6 = 0.078.

This estimate contains considerable error. One error is that the

observed average exposure duration preceding diagnosis in the workers is an underestimate of the true biological latency. There are two reasons for this statement:

a. The number of people in the industry has increased steadily since 1940. Therefore the current work force contains an over representation of people with short exposure times, and the cases which have appeared are systematically biased toward short exposure times.

b. Even if the number of exposed people had not increased in the past, the disease could still develop in those people in the future, which would result in a longer average exposure duration before diagnosis.

A more fundamental difficulty in attempting a comparison of exposure times for rats and humans is the uncertainty whether the disease is caused by a gradual build-up of some type of tissue irritation which requires constant intake of vinyl chloride or whether it is caused by an event occurring randomly in the exposure history and progressing to angiosarcoma independent of subsequent exposures. Intuitively, we think the latter mechanism may be happening in animals because of the independence of latency time with respect to dose. However, in people, there is evidence of latency time variation with dosage (see reference 7). If there are indeed different mechanisms in rats and people the ratio of exposure durations computed above has no valid interpretation.

Latent time considerations would dictate that the annual incidence of human cases should be 0.078 times the annual incidence of rat tumors. The model in Appendix B assumed a factor 0.033, so that exposure duration considerations would dictate that the rates calculated from the model should be multiplied by 2.4.

One intuitive measure of the sensitivity of a species is to compare for similar doses, the time it takes to get cancer, expressed as a fraction of total lifespan. For rats this is 80/100 = 0.8 of a lifetime irrespective of dose and for humans it is 19.6/72 = 0.27 of a lifetime. By this measure, humans are over three times more sensitive than rats.

Comparison of Angiosarcoma Incidence

The estimation of liver angiosarcoma incidence in workers is possible from several epidemiology studies, but unfortunately the only study in which it was possible to define the vinyl chloride exposure (reference 4) had too small a sample size to detect liver angiosarcoma cases.

In this plant, measurements of vinyl chloride sampled in the breathing zone of the workers were begun in 1950, and continued until the

present. It was found that in an old section of the plant, exposure in the wet end operations averaged 120-385 ppm, over an 8 hour/day 5 day/week time period, with documented excursions up to 4000 ppm. The measured excursions coincided with reports of workers feeling dizzy on the job. In 1959, following reports of toxicological effects of vinyl chloride, the operations were improved, a continuous monitor was installed and subsequent exposures for the same job were reduced to 20-80 ppm with excursions of 500 ppm. In a newer section of this plant the highest exposure job was 135-825 ppm before 1959 and 30-240 ppm thereafter.

Since this is one of the largest companies and one of those most concerned with worker exposure, it is likely that these are lower than the industry average, so that one might assume from this that the cases of angiosarcoma occurring among workers in the last 5-10 years were the result of past chronic exposures of 200-500 ppm.

In Table 1 the incidence of angiosarcoma from several industrial studies is summarized. The Tabershaw-Gaffey study (reference 5) of records of 8384 men in the entire vinyl chloride industry classified 1817 of them in the high exposure, high duration category. Since the study encompassed 33 plants, it was not possible to define objectively what "high" exposure was, but instead each plant classified cases high or low considering only its own experience. The term "high duration" here means more than 60 months on the job. They found two angiosarcomas in the 1817 people, but from detailed studies by other investigators an additional four were found to be misclassified as other diseases, so that the incidence of angiosarcoma among the high exposure, high duration workers was found to be $6/1817 = 3.3 \times 10\text{-}3$. The average exposure duration for this group was 15.9 years.

Nicholson et. al. (reference 6) studied 255 workers employed in one plant for more than 5 years. Of these, 151 worked in direct PVC production and 3 cases of liver angiosarcoma were found in this group for an incidence of 20 X 10-3. They were exposed for 14, 17, and 23 years respectively. The exposure duration for the entire 255 workers ranged from 5 to 28 years, and most of them were exposed for more than 23 years.

In the Heath and Falk study (reference 7) of angiosarcoma cases in the Louisville plant, 7 cases were seen among 270 people working directly in polymerization activities, for an incidence of 26 X 10-3. The mean duration of exposure (employment) was 17 years in the seven cases. The authors stated that these 270 workers represent about 20% of the plant employees.

The study of J. K. Wagoner (reference 8) of 745 male workers in two plants, 31 cancer deaths, 6 of them liver cancer were reported. This population of workers had been engaged in the polymerization of vinyl chloride for at least 15 years. The type of liver cancer was not specified, so that this study can yield only an upper limit of the liver

angiosarcoma incidence; it is less that 6/745 = 8 X 10-3. Since no breakdown of job categories was made in this study it is likely than many of the 745 people did not have the highest exposure tasks.

In comparing the incidence in table 1, it is significant that studies with the larger number of people have the lowest incidence and the studies with the most complete definition of worker exposure have the highest rate. It can be concluded that the incidence among just the most highly exposed workers is about 0.02.

The incidence numbers in Table 1 represent the number of cases diagnosed before 1974 divided by population exposed before 1974. These numbers, however, do not really represent the true incidence of the disease because all members of the population exposed before 1974 have not had time to develop angiosarcoma because of its 17-year average exposure duration. At least two alternative approaches are available to adjust for latency time effects. The first approach described in this paragraph assumes a fixed exposure duration and considers only the population exposed earlier than this time. The second approach described in the next section considers the entire exposure duration distribution. In the first approach the incidence is expressed in terms of the population exposed before 1974-17 = 1957, which is only a fraction of the population exposed before 1974. To calculate this fraction, information concerning the number of people entering the work force as a function of time from reference 5, table 2 has been used. It is found that the ratio of people whose exposure began before 1974 to the number whose exposure began before 1957 is 3.8. Therefore the population in which cases of angiosarcoma have appeared is 1/3.8 as much as the population in table 1, and the incidence among workers is 3.8 times that given in table 1, or 0.02 X 3.8 = 0.076. This means that sometime in their lives, over 7.5% of all highly-exposed workers are expected to get liver angiosarcoma.

The average exposure time for high duration workers reported in the industry-wide Tabershaw-Gaffey report (reference 5) is 16 years. Therefore, the incidence rate, defined as the number of cases per person-year of exposure, is 0.076/16 = 0.00475 per person-year.

Alternative Approach to Calculating Incidence Rate

The difficulty with the previous approach is that a fixed exposure duration was assumed whereas the actual distribution of exposure durations is approximately normally distributed in log (duration) for the 14 reported occupationally-exposed cases. For each year, t, of exposure, n(t) person-years of exposure have occurred, and the number of cases, c(t), that have occurred before 1974 due to the exposure at time t is

$$c(t) = n(t)\ p\ L(74-t)$$

where p is the probability per person-year of exposure that a person

will get angiosarcoma sometime in his life after being exposed for one year, and L(74-t) is the probability that the exposure occurred a long enough time ago to appear by 1974 if he was exposed in year t. The function L (x) is the cumulative distribution of latency times and is equal to the probability that the latent time is less than or equal to X years. The total number of cases is the sum of c(t) over all times from the beginning of exposure to times so recent that L (74-t) is vanishingly small. For convenience we shall write n(t) as the product of the total number of person-years of exposure, N, and a distribution function, q(t) which is the fraction of the N person-years that occurred in year t. With these quantities defined, the probability p can be calculated from

$$p = \frac{\sum c(t)}{N \sum q(t) \times L(74-t)} \qquad (1)$$

For this calculation the function q(t) was derived from table 2 of the Tabershaw study (reference 5), where the distribution of man-years of employment is presented as a function of the year in which exposure started. It is assumed that the distribution of man-years is the same for highly-exposed employees as for all 7128 workers in his study. The distribution of exposure durations for the 14 known occupational cases of liver angiosarcoma was taken from reference 2 and used for L(74-t). With these functions, the cumulative product in the denominator of equation (1) is 0.378. This is the fraction of cases which have been initiated by exposure through 1974 which have been diagnosed.

Therefore the overall effect of this more exact treatment, where the exposure duration distribution is explicitly considered, is to multiply the calculated probability by 1/0.378 = 2.65. This turns out to be not much different than the earlier approach, where the factor was 3.8. We consider the alternative approach to be conceptually more firmly based. Therefore we obtain 0.02/(17 X 0.378) = 0.0031 as the probability per year of exposure that a highly-exposed worker will get angiosarcoma sometime in his life. The errors in this calculation are of two types: (a) uncertainties in the numerical estimates of parameters; and (b) conceptual errors in the assumptions of the model. The first type can be quantified in the following way. The chronic dose experienced by highly-exposed workers is estimated to be somewhere between 200 ppm and 500 ppm. The value of 350 ppm was chosen as the mid-point of that range, so the variation could be $\pm$ 150 ppm, or $\pm$ 43%. Although this error does not strictly enter into the calculation of the 0.0031 value, it does contribute to the error when this is compared with the animal data, as discussed on page D-6. The incidence of angiosarcoma in highly-exposed workers was 0.02 (table 1) and by intuition the author would guess that it should be within the range of 0.01 or 0.03, for a variation of 50%. The number of hours of daily exposure in the workers is almost certainly not as much as 8, but may well be over 6 hours, so one may say it is 7 $\pm$ 1 or 7 $\pm$ 14%. If we assume that these errors are random, the error in the product of these factors is

$$\sqrt{(0.43)^2 + (0.50)^2 + (0.14)^2} = 0.67$$

The conceptual errors in the assumptions of the model are not directly quantifiable. One error is that we assumed no breaks in exposure once employment began. People who left the job and returned later have contributed their man-hours of exposure more recently than we assumed, and would therefore not contribute as much to the occurrence of cases observed today. This has caused us to over-estimate the incidence. A second error is that, as discussed on page D-2, the distribution of latent times is biased toward shorter exposure intervals than is likely to be the actual case. The error acts in the same direction as the first, and would cause a further over-estimate of the incidence.

A third error is that the true biological latent time is not directly observable, since the process leading to irreversable disease may have been initiated some unknown time after the first year of exposure. By using the duration of total exposure, we tend to over-estimate the true biological latent time. This error operates in a direction opposite to the preceding two errors. The net result of these of these three errors is unknown in direction or size.

The overall conclusion is that the incidence rate is 0.0031 per person-year of exposure with a quantifiable error due to uncertainties in estimation of parameters of 67% and an additional unknown conceptual error in the precise assumptions.

It is important to point out that the incidence rates calculated in this Appendix are probabilities based on the duration of exposure to vinyl chloride, rather than on the number of cases which happen to be diagnosed in a population each year. In descriptive epidemiology the latter concept is called the incidence rate. The epidemiological incidence in the general United States population is discussed in Appendix E.

Comparison With Animal Data

At this point we are in a position to compare the human annual incidence rate (0.0031) with that predicted from the animal model in Appendix B. For continuous exposure to 350 ppm, Appendix B would predict an incidence rate of $(0.071 \times 10^{6}) \times 3.5 \times 10^{5}) = 0.0249$ per person-year of exposure. If this is adjusted to occupational exposure conditions by dividing by $(24 \times 7)/(7 \times 5) = 4.8$, the incidence rate for highly-exposed occupational groups is predicted to be 0.0052 per person-year of exposure. This is a factor of 1.68 higher than the human rate. Therefore all of the estimates in Appendix B should be multiplied by 1/1.68 = 0.60 to be consistent with the human data. When the error estimates are explicitly taken into account, we find for the animal model, that the range encompassed by plus or minus one standard error is $(0.0052 \pm 27\%) = 0.0038$ to 0.0066 and for the human data it is $(0.0031 \pm 67\%) = 0.0010$ to 0.0052. Therefore, within the accuracy of our procedures, the two approaches for calculating the incidence are in agreement.

The rationale for comparing human incidence data with the rat experiments is considered more firm than the alternative approach of comparing latency times, as discussed on page D-1, because of the conceptual difficulties already pointed out.

The other effects of vinyl chloride besides liver angiosarcoma are evaluated in the remainder of this appendix.

Ratio of all cancers to liver angiosarcoma

The study of Nicholson, et al. (reference 6) showed that out of 255 workers 24 deaths were recorded, 9 of them were due to cancer, 3 of which were liver angiosarcoma. Unfortunately this study cannot be used to estimate the number of non-angiosarcoma cancers caused by vinyl chloride because if the 3 angiosarcomas were not in the population, there would be 6 cancers out of 21 deaths, which is not different than one would expect in the general population. Reference 15, p. 2 indicates that of all deaths in the general population, 1/5 of them are due to cancer.

In the Tabershaw study of mortality in the VC-PVC industry (reference 5) the cancer mortality of the high exposure group is only slightly higher than the overall cancer mortality for the entire group. Although this slight excess could be due to vinyl chloride exposure, it is not enough to enable one to estimate how many cancers of all sites are induced relative to liver angiosarcoma.

Studies by Ott, et al. (reference 4) and Wagoner (reference 8) have shown statistically significant excesses in mortality from many primary cancer sites, including brain, respiratory system, and lymphomas. However, angiosarcomas were not observed, so that the ratios of total/angiosarcoma incidence cannot be estimated from these studies.

In a proportional mortality study of 161 workers in the Louisville plant, Monson, et. al. (reference 16) found a larger rate of cancers than expected for U. S. white males at the following sites: digestive tract (excluding liver), liver and biliary tract, lung and brain. They found 41 deaths due to all cancers (compared with 27.9 expected) for an excess of 13 cases. In the same population there were 5 deaths due to liver angiosarcoma (compared with a vanishingly small number expected). Therefore the total number of cancer deaths is 13/5 = 2.6 times the number of liver angiosarcoma deaths. One cannot be absolutely sure that all of the cancers in this population are due to exposure to vinyl chloride, but in view of the other studies cited above, it can be said that vinyl chloride is a strong risk factor in the development of other cancers. In the rat experiments of Maltoni, a total of 76 animals had Zymbal gland carcinomas and liver angiosarcoma combined, compared with 47 with liver angiosarcoma, for a ratio of total cancer/liver angiosarcoma of 1.62. When all tumors were considered in the Appendix B, the ratio was 2.0. Therefore, both the human and animal data show that vinyl chloride induces about twice as many total number of cancers as liver angiosarcomas alone.

Frequency of Non-Cancer Effects Relative to Liver Angiosarcoma

In a literature review of 12,724 vinyl chloride workers in the United States and Europe (reference 12) Marsteller, et al. found 118 cases of acroosteolysis (a gradual erosion of bone at the fingertips), 97 people with symptoms of Raynaud's syndrome (cold hands and feet), 40 people with skin legions, and 73 with liver disturbances. We might assume that, of these 328 cases of reported symptoms, 20% of the people had 2 symptoms each and the other 80% had one each, so that the total number of people reporting symptoms in 328/1.2 = 273 people. This incidence of overt symptoms ($273/12,724 = 21 \times 10^{-3}$) is to be compared with the incidence of angiosarcoma in a similar large worker population such as is seen in reference 5, Table 1, which is 3.3×10^{-3}. The ratio is 7 people with symptoms for every liver angiosarcoma case.

In detailed clinical observations of 50 highly exposed people currently working in plants, Marsteller (reference 12) finds that only one had a history of liver disease and 8 had experienced Raynaud's syndrome. Despite this lack of overt symptoms, he found that 38 of the 50 had pathologically high BSP retention times (a measure of serious cellular liver damage), 31 had marked liver enlargement, which could be palpated, and 42 had abnormally low blood platelet counts. Therefore for every person with clinical symptoms of vinyl chloride exposure there is expected to be $38/9 = 4.2$ people with liver malfunction serious enough to cause abnormal BSP retention times. This brings the ratio of serious liver malfunction to angiosarcoma to $4.2 \times 7 = 30$.

The frequencies of abnormal BSP measurements and low platelet counts seen by Veltman (reference 13) in 70 vinyl chloride workers are almost identical to those found by Marsteller, but Veltman found only half the frequency of Reynaud's syndrome.

In a liver function screening program among 1183 workers at Louisville, Creech and Makk (reference 14) used a large battery of blood chemistry tests of liver function followed by more elaborate diagnosis of people who were abnormal in the initial screen. In this series of tests, 59 people were found to have liver function abnormalities; 17 of them major abnormalities which required biopsies and other elaborate tests. The plant physicians considered the 59 cases abnormal enough to justify moving the people to work areas where there were no hepatic toxins. Of the 17 serious cases, 2 turned out to be liver angiosarcoma. Therefore from this study, the ratio of definitive liver toxicity to liver angiosarcoma cases is $59/2 = 30$, a ratio which agrees with the literature survey of Marsteller, et al. (reference 12).

TABLE 1 - LIVER ANGIOSARCOMA INCIDENCE AMONG HIGHLY EXPOSED WORKERS

Reference	Number of Angiosarcoma Cases	Number of People Surveyed	Incidence ($\times 10^{-3}$)
5	6	1,817	3.3
6	3	151	20
7	7	270	26
8	<6	745	<8

REFERENCES FOR APPENDIX D

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Appendix E

Is Residence Near Vinyl Chloride Plants a Risk Factor In Frequency Of Deaths Due To Liver Angiosarcoma?

I. Introduction

Abundant evidence exists that vinyl chloride is one of the chief causative factors for the high frequency of liver angiosarcoma among highly-exposed workers in the vinyl chloride-polyvinyl chloride industry. In proposing to regulate air emissions around these plants on the basis of health hazards to people living near factories, it is important to look for evidence that this disease occurs more frequently among people living near plants than those living at random places in the United States. Accordingly an investigation was made of the place of residence, relative to the vinyl chloride and polyvinyl chloride plants which are covered by the proposed regulation, of the people who thus far are known to have contacted liver angiosarcoma.

II. Sources of Data

A. Plants and Locations

The list of plants and their addresses which was used in the investigation is shown in Table I. It was compiled from the APHA report (reference 1) and the EPA Air Programs Office document (reference 2). This list includes some plants that are no longer in operation and at least one plant which is reported (by APHA) to involve no current work with vinyl chloride. Some of the plants make co-polymers with vinyl chloride and other monomers. The list is believed to include all plants in the contiguous states which make vinyl chloride monomer or polyvinyl chloride resin. The fact that it contains extra plants does not detract from this study; in fact it might be desirable to expand the investigation to all plants known to fabricate plastics if it were not for difficulty that such an expansion would excessively broaden the list of chemicals which could be implicated as causal agents.

In several cases street addresses of the plants are not available. In these cases it was assumed that the plant was somewhere within the city limits of the postal address (for large cities) or was exactly at the center of town (for small towns or suburbs with no definite boundaries).

B. Liver Angiosarcoma Cases

In September 1974, Dr. Henry Falk of the Cancer and Birth Defects Section, Center for Disease Control (CDC) initiated an extensive case-finding national survey of all liver angiosarcomas which have been

diagnosed between 1964 and 1974. He obtained the information from three sources:

(1) A systematic examination of death certificates filed at the National Center for Health Statistics, Research Triangle Park, N. C. Copies of death certificates were obtained for those deaths where the diagnosis was similar to, or could easily be confused with, liver angiosarcoma. Death certificates always give date and place of death, age, sex and race, date (and frequently place) of birth, residence and occupation at time of death, occasionally the time lived at the residence, the immediate and underlaying cause of death and a statement of whether an autopsy was performed.

(2) Case records on file with the Armed Forces Institute of Pathology. These included cases diagnosed at military hospitals. Usually residence and occupational information were not provided, and for the most part only age, sex, hospital location, autopsy number and a minimum amount of clinical information were available from this source.

(3) Response to requests for information originally sent out by Dr. Falk to state public health departments and hospital pathologists throughout the nation. Typically a letter from a state official would list cases on record and Dr. Falk would send letters to the pathologists identified by the state requesting further information and permission to contact physicians and patients. This process invariably results in complete clinical histories of the patients, (dates of hospital admission, description of methods of diagnosis, detailed surgical and autopsy reports) but rarely includes more than a bare minimum of personal information such as residence and occupation.

Currently Dr. John Herbert at CDC is continuing the investigation by interviewing next of kin and physicians in order to get residence, occupational and medical histories, family members with cancer, possible exposure to other chemicals through home hobbies, drinking and smoking histories and any other personal information which could indicate causal connection with the disease. As of early October, Dr. Herbert has followed up about 20 cases in this way.

In order to confirm the initial diagnosis of liver angiosarcoma, Dr. Louis B. Thomas, Director, Pathology Laboratory, National Cancer Institute has agreed to examine the sections of tissue which CDC obtained from the hospitals. This confirmation is regarded to be absolutely essential, especially when attempting to draw conclusions from a small number of cases. The information currently on hand is far from complete. As of early October 1975, a large backlog of slides was awaiting confirmation at the NCI and over 90% of the cases have not yet been followed up by CDC.

III. Procedures of this Study

With the cooperation of Dr. Herbert, the author, assisted by Dr. Kenneth Cantor, went to CDC and extracted the available information on liver angiosarcoma cases. The form shown on Attachment A was filled out to the extent possible for each case in the files. To maintain confidentiality of personal information, the names of the deceased were not copied from CDC records. Instead the cases are identified in our files by state and initial letters of the name.

A total of 286 cases were identified. Out of this total the cases with information on place of residence at time of death were selected; this group was further examined and cases with known or suspected exposure to arsenicals or thorotrast and cases of known occupational exposure to plastics fabrication and VC-PVC favrications were eliminated. A subsample of the entire group of 286 cases was analyzed for age and sex distribution and tested on a state-wide basis for clustering to a greater degree than expected on the basis of population concentration.

Following the case selection procedure, the place of residence of all selected cases was identified using maps and atlases of various scales.

The initial survey of residences was done by locating cities and towns in an encyclopaedia atlas (reference 3). This was found to be adequate to locate residences to within 10 miles from plant locations. In cases that were suspected to be within 10 miles of the plant, indexed street maps were consulted at the Geography and Map Division, Library of Congress, Alexandria, Virginia.

The plant locations had been identified on a series of U.S. Geological Survey topological maps (scale of 1: 250,000, or 10 statute miles = 6.4 cm) by Teknekron, Inc. under contract with EPA's Office of Planning and Evaluation. These plant locations were verified by detailed street maps at the Library of Congress, for those plants where residence of cases was less than 10 miles from the plants.

IV. Results of the Survey:

Of the 286 case records obtained from CDC, all cases from the states alphabetically from A through M (a total of 166 cases where age and sex is known) were analyzed for age distribution and sex ratio and a test of gross clustering was performed. Such analysis for the entire population of 286 cases will be performed at a later time. It was found that of the 166 cases, 119 were males and 47 females, for a sex ratio of 2.5 males/1 female. The age distribution for females is approximately constant for all ages. It is more variable for males, but there are not obvious bimodalities. When the male/female sex ratio is examined at a function of age, it is found that for all cases less than age 44, the ratio is about 1.0 (27 males/20 females), but for ages above 45 it is larger than a factor of three.

An X^2 test was performed to test the hypothesis that the number of cases in each state is proportional to the 1970 population of the state. If the data should disprove the hypothesis, we would have evidence of large-scale (state-wide) clustering of cases which cannot be explained by population concentrations. The results were that (for the states A through M) X^2 was no larger than chance variation would predict, so that there is no evidence of clustering on a state-wide scale.

Of the 286 case records obtained from CDC, 176 cases remained after elimination of those with no residence information and possible thoratrast, arsenical, and occupational VC exposures. The rejected cases included 12 possible thoratrast exposures, two possible arsenical exposures, one person exposed occupationally to plastics, and six cases from Alaska and Hawaii.

After locating the residence cities and towns of the 176 cases using an United States Atlas, there were only a handful of cases close enough to the plants to justify searching the detailed maps at the Library of Congress. Cases of distances larger than 20 miles from the plant were only rarely recorded, and to date a complete tabulation of number of people versus distance in the range of 5 to 20 miles of all plants has not been made. However, for distances less than five miles, there were only six cases, as shown in Table II.

Case number 1 of Louisville, Kentucky appears on this list through a clerical error because by mistake his work address was traced and found to be less than 5 miles from the plant, whereas the home address is the subject of this study. This accident does cause one to speculate whether a systematic investigation of employees working near vinyl chloride plants would reveal some larger than expected rates of angiosarcoma. It also emphasizes the importance of locating place of occupation in the case of follow-up.

Cases 2 and 4 must be eliminated as candidates for vinyl chloride induced liver angiosarcoma caused by living close to factories. Case 2 moved from Egypt to Jersey City just two years before his death. Cases 4 and 5 turned out to be other types of cancer, according to NCI pathologists.

It is still possible that Cases 1, 3, 5 and 6 can be attributed to residence near vinyl chloride plants, but we will not know until NCI confirms or denies the diagnosis, and until there is more complete follow-up of the residence history of Case 6.

Case 6 is a special situation because he was an infant who died at 5 months of age from a liver cancer which is relatively common among infants. This case must be eliminated from the formal study because it is not a liver angiosarcoma. It could have been caused by vinyl chloride, but we have no knowledge of any facts about the parents except residence at the time of their son's death. Since transplacental carcinogenesis has been observed in animal studies, it is possible that Case 5 is a case of cancer caused by residence close to a vinyl chloride plant.

V. Discussion of Results

Liver angiosarcoma is an extremely rare disease among the United States population. According to data in the Third National Cancer Survey (reference 4) the incidence rate averaged over the nation is 0.0128 per 100,000 population per year. At this rate, the expected yearly incidence in the United States population (203 million people) is 26 per year, and the expected incidence among the 4,580,000 people living within 5 miles of the plants listed in Table I is 0.59 cases per year. Therefore for the 10 year collection of cases in the CDC files we would expect 5.9 cases to occur within 5 miles of all plants if the presence of the vinyl chloride plant contributed no risk factor pre-disposing people to the disease.

The number of cases in our study, 286, is close to the expected 10 year total of 260, and the 3 possible angiosarcoma cases within five miles of vinyl chloride plants would probably match well with the 5.9 cases expected if we could get residence information and trace addresses for the cases in which we have no information. Since we could only trace 176 of the 286 cases, the approximate number of cases close to the plant would total 3 X (286/176) = 4.9 if all were traced. For these reasons our files probably contain most of the cases actually recorded in these ten years.

The high male/female sex ratio and the striking manner in which it increases above age 45 are indications that this is an occupationally-exposed population, and there may be other factors in addition to vinyl chloride.

This survey has produced no evidence that living around vinyl chloride plants is a risk factor in the occurence of liver angiosarcoma. This conclusion is far different than saying that living around plants is not a risk factor for several reasons: 1) this type of survey of a disease with a latent time from first exposure to diagnosis of 17 years reflects exposures that started at some time before 1957, when the quantities of vinyl chloride produced were much smaller than the current production levels. 2) This survey did not include the place of occupation of the currently-suspected collection of liver angiosarcoma cases. Therefore it underestimates the risk of being near a vinyl chloride plant. 3) This survey might not have detected all existing liver angiosarcoma cases, although the number we have is consistent with the national statistics. The circumstantial evidence for this is that there was not substantial overlap between the three sources of case information. If the data sources had been complete, the information collected by CDC from the National Center for Health Statistics would contain all the cases

reported by both the Armed Forces Institute of Pathology and the state health departments. 4) In over 90% of the cases traced in this survey, the only information available was the residence at the time of death, and in some cases, the residence of the spouse or parent only. This information is only a crude indication of where the individuals spent most of their lives. 5) In contrast with our expectation when the survey was started, there is a significant rate of changes in diagnosis after the slides were confirmed by the National Cancer Institute. The 286 cases currently on file cannot be regarded as definitely-established liver angiosarcomas.

In view of these limitations of the survey, positive statements cannot be made about residence near plants being or not being a risk factor. The only interpretation of these results that is justified is that a search was made of the residence information which exists and this search revealed no evidence that residence near plants is a risk factor. In view of the long 17-year latent time it is expected that any survey of current cases would underestimate the actual risk.

Table I: List of VC-PVC Plants and their Locations

Company	Type VC/PVC)	Location
1. Air Products and Chemicals, Inc.	PVC	Pace, Florida
2. Air Products and Chemicals, Inc.	PVC	Highway 95 Calvert City, Ky.
3. Allied Chemical Corp.		near River Mile 2355 Gulf State Road Baton Rouge, La.
4. Allied Chemical Corp.	VC	Geismar, La.
5. American Chemical Corp.	VC, PVC	Long Beach, Calif.*
6. Atlantic Tubing & Rubber	PVC	Cranston, R.I.*
7. BAST Wyandotte		500 Central Ave. S. Kearney, N. J.
8. Borden, Inc.		Geismar, La.
9. Borden, Inc.		Bainbridge, N.Y.*
0. Borden, Inc.		Compton, Calif.*
11. Borden, Inc.		Demopolis, Ala.*
12. Borden, Inc.	PVC	Illiopolis, Ill.
13. Borden, Inc.	PVC	Leominster, Mass.*
14. Borden, Inc.		near 59th & Interspace St. Oklahoma City, Okla.
15. Continental Oil Co.		Lake Charles, La.
16. Continental Oil Co.	VC	Old Spanish Trail Westlake, La.
17. Continental Oil Co.	PVC	Aberdeen, Miss.
18. Diamond Shamrock Corp.	PVC	River Road Delaware City, Dela.
19. Diamond Shamrock Corp.	VC, PVC	La Porte Highway Deer Park, Texas

Company	Type (VC/PVC)	Location
20. Diamond Shamrock Corp.		Plaquemine, La.*
21. Dow Chemical Co.	VC	Freeport, Tex.
22. Dow Chemical Co.	VC	Oyster Creek, Tex.*
23. Dow Chemical Co.	VC	Plaquemine, La.
24. Dow Chemical Co.	PVC	Midland, Mich.
25. Ethyl Corp.	VC, PVC	Gulf State Road Baton Rouge, La.
26. Ethyl Corp.	VC	Deer Park, Tex.
27. Firestone Tire & Rubber Co.	PVC	Firestone Blvd. Pottstown, Pa.
28. Firestone Tire & Rubber Co.	PVC	Perryville, Md.
29. Foster Grant Co.		389 N. Main Street Leominster, Mass.
30. General Tire Co.	PVC	Ashtabula, Ohio
31. B. F. Goodrich Co.	PVC	Walker & Moore Road Avon Lake, Ohio
32. B. F. Goodrich Co.	PVC	2104 E. 23rd Street Carson City, Calif.
33. B. F. Goodrich Co.	PVC	41st Street & Bells Lane Louisville, Ky.
34. B. F. Goodrich Co.		188 Presidio Place Williamsville, N. Y.
35. B. F. Goodrich Co.	VC	near River Mile 17 Tennessee River Calvert City, Ky.
36. B. F. Goodrich Co.	VC	Henry, Ill.
37. B. F. Goodrich Co.	PVC	Pedrickstown, N. J.
38. Goodyear Tire & Rubber Co.	PVC	Plaquemine, La.

Company	Type (VC/PVC)	Location
39. Goodyear Tire & Rubber Co.		5408 Baker Avenue Niagara Falls, N. Y.*
40. W. R. Grace & Co.		Owensboro, Ky.*
41. W. R. Grace & Co.		South Acton, Mass.*
42. Great American Chemical Corp.	PVC	Fitchburg, Mass.*
43. Keysor-Century Corp.	PVC	2600 Springbrook Avenue Saugus, Calif.
44. Monochem, Inc.	VC	Geismer, La.*
45. Monsanto Co.	PVC	730 Worchester Street Indian Orchard, Mass.
46. Monsanto Co.		Texas City, Tex.
47. Morton Norwich Co.		Ringwood, Ill.*
48. National Starch & Chemical Corp.	PVC	Meredosia, Ill.*
49. Occidental Petroleum Corp.	PVC	River Road Burlington, N. Y.
50. Occidental Petrolium Corp. (Hooker Chemical)	PVC	New South Road Hicksville, N. Y.
51. Olin Corporation	PVC	238 S. Main St. Assonet, Mass.*
52. Pantasote Co.	PVC	26 Jefferson Street Passiac, N. J.
53. Pantasote Co.	PVC	Point Pleasant, W. Va.*
54. Pittsburgh Plate Glass Industries, Inc.	VC	Columbia Southern Road Lake Charles, La.
55. Robintech, Inc.	PVC	786 Hardy Road Painsville, Ohio
56. Shell Oil Co.	VC	State Highway 225 Deer Park, Tex.
57. Shell Oil Co.	VC	Norco, La.*

Company	Type (VC/PVC)	Location
58. Schintech	PVC	Freeport, Tex.*
59. SCM Corp. (Huron Plastics)		Huron, Ohio
60. Stauffer Chemical Co.		2112 E. 223rd Street Carson City, Calif.
61. Stauffer Chemical Co.	PVC	Delaware City, Del.*
62. Stauffer Chemical Co.		School House Road Burlington, N. J.
63. Tenneco Chemicals, Inc.	PVC	Beverly Road Burlington, N. J.
64. Tenneco Chemicals, Inc.	PVC	Flemington, N. J.*
65. Tenneco Chemicals, Inc.	VC	Painesville, Ohio
66. Tenneco Chemicals, Inc.	VC	4403 La Porte Road Pasadena, Tex.
67. Union Carbide Co.	PVC	4337 McCorkle, South Charleston, W. Va.
68. Union Carbide Co.	PVC	Highway 146 & Texas Avenue Texas City, Texas
69. Union Carbide Co.		Taft, La.
70. Union Carbide Co.	Reported Closed	Niagara Falls, N. Y.*
71. Uniroyal Inc.	PVC	720 Fairport Nursery Road Painesville, Ohio
72. Vulcan Materials Co.		Geismar, La.
73. Vulcan Materials Co.	VC	Deer Park, Texas*

*Location not included in APHA estimate of total population.

ANGIOSARCOMA WORKSHEET

CDC #: _____ Name: _____ Sex: _____

Death Certificate: Place of Death: _____ Date of Death: _____

Biopsy Performed: Yes /__/ No /__/ Date of Biopsy: _____

Autopsy Performed: Yes /__/ No /__/ Date of Autopsy: _____

Specimens Available: Yes /__/ No /__/

Diagnosis: _____
(Immediate Cause)

_____
(Underlying Disease)

Date of Birth: _____ If not known: Age (at biopsy): _____

Age (at autopsy): _____

Age at Death: _____

Date of Diagnosis: _____ Age at Diagnosis: _____

Residence at Time of Death: _____

Occupation at Time of Death: _____

Family: Married: Yes /__/ No /__/

Children: Number: _____ Ages at Death: _____

Pathology Reviews:

Specimens Received: Yes /__/ No /__/ Unavailable /__/

Specimens Reviewed: Yes /__/ No /__/

NIH Report: _____

AFIP Report: _____

CDS Report: _____

Followed up by CDC: Yes /__/ No /__/

CDC #: _____ Other Patient I.D.: _____

Occupational History

	Name of Employer	Address	From	To	Job Title	Job Description	VC As	Other Chemicals
1.								
2.								
3.								
4.								
5.								

Residence History

	City, State	Address	From	To	Distance from VC Plant	Distance from Other Industry
.						
.						
.						
.						
.						

embers of family exposed via occupation or residence? Yes /__/ No /__/ If yes, use additional sheet.

Table II Case Summary

Case Identification	Distance from Plant	Time in Area	Age at Death	NCI Confirmation
1. JLK, Louisville Kentucky	Home: 6.7 mi. SSW of B. F. Goodrich Work: 4.3 mi. ESE of B. F. Goodrich	32-1/2 years	33	No
2. IN, Jersey City, New Jersey	Home: 2.0-2.4 mi. SE of BAST Wyandotte	2 years	41	No
3. HCM, Buffalo	Home: Age 0-20: Distance 7-9.2 mi SW of B.F. Goodrich 20-40: 2.6-4.4 mi. WSW of B.F. Goodrich 40-58: 8-9.5 mi. SSW of B.F. Goodrich 58-68: 3.8-5.2 mi. SW of B.F. Goodrich	68 years	68	No
4. CF, Niagara Falls	Home: 0.25 to 1.1 mi. SSE of Goodyear	30 years	63	Yes, not angiosarcoma
5. GB, Niagara Falls	Home: 0.25 to 1.0 mi. NNW of Goodyear	5 months	5 mo.	Yes, not angiosarcoma
6. RJ, Niagara Falls	Home: 2.1-2-2.3 mi. W of Goodyear	?	41	No

Appendix E References

1. Landau, E., "Population Residing Near Plants Producing Polyvinyl Chloride," American Public Health Association, Contract report, EPA/OTS (August 1975).

2. EPA, OAQPS, Emission Standards and Engineering Division, "Standard Support-Environmental Impact Statement, Vol. II (draft)." April 1975.

3. Encyclopaedia Britannica, "Britannica Junior, Vol. 15" (1959).

4. National Cancer Institute Monograph 41, "Third National Cancer Survey: Incidence Data," March 1975.