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Brief Summary

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U.S. ENVIRONMENTAL PROTECTION AGENCY PROPOSED AMENDMENTS TO THE NATIONAL EMISSION STANDARD FOR VINYL CHLORIDE

COMMENTS BY THE

HEALTH COMMITTEE
POLYVINYL CHLORIDE SAFETY GROUP
THE SOCIETY OF THE PLASTICS INDUSTRY, INC.

R&S 113449

APPENDIX I.

Health Subcommittee Comments on Proposed Vinyl Chloride Standard

A.

INTRODUCTION

These comments have been prepared by the Health Committee of the Vinyl Chloride and Polyvinyl Chloride Producers Group of SPI. The Committee has analyzed the Scientific and Technical Assessment Report on Vinyl Chloride and Polyvinyl Chloride ("STAR Document"), the Quantitative Risk Assessment Community Exposure to Vinyl Chloride ("Risk Assessment Document") and the Administrator's explanation preceding the proposed Vinyl Chloride Standard published in 40 Fed. Reg. 59523 et. seq. Our comments are divided into three parts: (A) an introduction and general critique of the documents as they pertain to public health matters; (B) a detailed discussion of certain specific objections; and (C) an appendix listing by page and line questions we have about parts of the documents.

At the outset, we believe that the Environmental Protection Agency has set for itself a high goal in the documents it has issued accompanying the proposed Standard. The STAR Document brings together in one place much of the information known about vinyl chloride and its health effects up to early 1975. The Risk Assessment Document is a necessary concept, and we applaud the approach of the Agency and hope that it will be used in the future. Our criticism is not with the process, which we endorse, but with some of the data, facts and interpretations drawn by the Agency.

1. Risk Assessment Document

Our principal criticism of the Risk Assessment Document is that at times it appears to be written to justify a conclusion already reached by the Agency rather than to set forth the scientific framework, and options open to the Administrator to make a difficult decision.

We believe a Risk Assessment Document should have two main purposes. First, it should assist the Administrator in reaching a decision about the wisest course to pursue in regulating chemicals such as vinyl chloride by identifying and attempting to quantify the various risks posed by the chemical and by describing the risk reduction which can be anticipated by various control techniques. Second, it should assist public understanding of the difficulties facing the Agency when it regulates a substance about which hard facts are unavailable and where extrapolation from existing data can be made only with limited reliability.

As will be set forth in greater detail we believe that the discussion of the "no threshold" assumption and the use of a "Log-Probit" model could have been more complete and objective. In all likelihood, such difficulties could have been solved if the Risk Assessment Document had been circulated in draft form and discussed with all interested parties before it was published. The Agency did so with most of the documents which were issued to accompany the Standard and in general, we understand that comments it received from interested parties were constructive.

If this process had been followed, we believe that the Risk Assessment Document would have presented a fairer and more complete discussion of the scientific background against which the Administrator's decision was made and would therefore have been of greater assistance to him and to the public in understanding his decision.

2. STAR Document

We also believe that some attempt should have been made to update the STAR Document when it was reissued in December. The information in that report was gathered almost twelve months prior to its final publication and in the intervening time certain additional information about the health effects of vinyl chloride had been gathered. For example, we understand from a statement by Dr. William Marcus that further investigation of so-called "community cases" was undertaken and that the Agency has concluded that there is no "evidence that angiosarcoma has been produced by vinyl chloride monomer in the general population." (Transcript, p. 42) We think this information should have been included.

We recognize that it is almost impossible to ensure that any scientific publication is absolutely current when it is published in the form of a STAR Document. However, in such cases, an errata or addendum could be issued at the time of its final publication and we urge the Agency to adopt such a procedure.

I. No Threshold Concept

The Risk Assessment's assumption of "no threshold" for a carcinogen is probably the most important assumption of the Document because it determines the mathematical model used in subsequent calculations. We believe that the Risk Assessment Document should have included the available evidence that VCM may have a threshold.

The Executive Summary flatly states "it is generally considered prudent to assume that there is no threshold for chemical carcinogens". That statement is not borne out by the text. On Page 3 the authors properly state that the no threshold assumption "is generally accepted as prudent in radiation carcinogenesis." They continue that for chemical carcinogenesis the model is usually considered to provide "an upper limit to the level of effects likely at extremely low doses...." See also B-2. We do not believe that the Risk Assessment Document should slide without further discussion from what is considered prudent in radiation carcinogenesis to what may be excessively cautious for chemical carcinogenesis.

The concept of "no-threshold" is in no way a universally accepted concept among scientists. There are numerous references in scientific literature to attest to the marked difference of

opinion among scientists: Dinman[1/], Stokinger[2/], Friedman, and many others have correctly pointed out that the body contains defensive detoxification mechanisms, which are capable of detoxifying and repairing low level responses to carcinogens.

There is even more specific evidence that the body contains certain defensive mechanisms capable of detoxifying VC and that there is a threshold for VC. Existing scientific data show that the routes of metabolism of vinyl chloride are markedly dependent upon the dosage inhaled or ingested. The data which were summarized at the February 3 hearing by Dr. P. J. Gehring are consistent with a threshold below which the body is able to handle small amounts of vinyl chloride without adverse effects. Dr. Gehring's testimony is now a part of the record, and we believe that if the Administrator is to accept the "no threshold" assumption, his decision should be discussed in a final document in the context of an empirical background which suggests that a metabolic threshold exists.

II. Log-Probit Model

The Risk Assessment Document accepts the linear dose-response model for purposes of determining the probability of developing angiosarcomas. Since individual susceptibility appears to be an

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1/ "Non-Concept" of "No Threshold" - Chemicals in the Environment, Burtram D. Dinman, Science Vol. 175, pp. 495-497, Feb. 4, 1975.

2/ Sanity in Research and Evaluation of Environmental Health, H. E. Stokinger, Science Vol. 174, pp. 662-665, Nov. 12, 1971.

important feature in the development of angiosarcomas in workers equally exposed to vinyl chloride, we think a log-probit model would have been more appropriate. Indeed, the authors of the Risk Assessment Document acknowledge that biological responses generally are better represented by a log-probit model. Apparently, ease of application and conservatism in approach caused rejection of what would otherwise have been a more appropriate model.

A more objective approach would have pointed out that the log-probit model fits more closely the Maltoni data, the only data which is cited for dose-response relationship.

Cases of liver angiosarcoma/experiment

Dose	Maltoni	Linear	Probit
50	1	.75	.99
250	4	3.74	4.13
500	7	7.47	6.85

In addition, the angiosarcoma-epidemiological data is also more consistent with a log-probit model. Based on the Third National Cancer Survey the crude incidence rate for the entire nation is 0.0128 per 100,000 population per year. The Risk Assessment Document used this rate to estimate the expected incidence of angiosarcoma within five miles of PVC and VCM plants studied as 0.59 cases per year giving a total of 5.9 cases for the ten-year period of the Study. Using the Risk Assessment Document's projections there were an estimated 4.9 cases within the five mile radius for the ten-year period. If we then take the authors' estimate of one excess case per year for the past ten years (See p. 7) and add it to the 5.9 figure established from the Survey, we would expect 15.9 angiosarcomas for the ten year period. In actuality by

extrapolation only 4.9 cases were found. The probability of finding five or fewer cases when almost 16 were expected is less than two chances in 1000 (.002), using the Poisson approximation. The epidemiological survey results do not fit the linear dose-response model, and we believe are further evidence that the log-probit model would have been more appropriate.

We also do not believe the Study should state that "the two approaches give results that are indistinguishable" (P. ii). This is just not the case at the tails of the curve which are the sectors of concern in this Standard.

Use of a log-probit model would have given the Administrator an option which on the face of the document was not brought to his attention. The Administrator assumes that the controls which must be adopted on promulgation of a final standard similar to the proposed one will reduce emissions by 95%. Implicit in the acceptance of this emission reduction and the use of a linear model is the Agency's acceptance that the standard imposed by Section 112 is met by a reduction of risk of 95%. If the Log-Probit model is used, however, the same percent reduction in risk, albeit to a much lower absolute value, can be attained by an emission reduction of 70%.[3/] Since the costs of

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3/ Using the Maltoni data, the linear model gives a rate of 4×10^{-6} at an assumed concentration of 17 ppb in the ambient air. To effect a 95% reduction in risk using that model the concentration must be reduced by 95% to 0.85 ppb. The log-probit model gives a rate of 0.04×10^{-6} using the same data. To reduce the rate by an equivalent amount ($0.04 \times 10^{-6} \times 0.05 = .002 \times 10^{-6}$), concentrations in the ambient air need to be reduced from 17 ppb to 4.6 ppb.

emission controls usually increase exponentially as the levels of emission are reduced, we think this information should be called to the Administrator's attention before he imposes a standard which he admits will cost $200 million in initial capital and over $70 million annually to operate.

III. Diffusion Model

The Agency has attempted utilizing a standard diffusion model to illustrate the benefits of the proposed standard and the anticipated risk to the general population within a 5 mile radius. However, the calculations do not support the degree of risk to which the Risk Assessment Document concludes the public is exposed and should be revised before a final Standard is promulgated.

The only results presented in the Standard Support Document are the calculations of the maximum concentrations predicted. These are not helpful in understanding the possible exposures of residents because, with one exception, these maxima occur at 80 meters from the source center, or within the plant boundaries in most cases. Some "typical" isopleths are given in the Risk Assessment Document, Appendix A, but the basic data used for these calculations are not specified.

The assumptions used in the calculation of the maxima are given, which overstate the possible exposure to vinyl chloride.

1) An average wind speed of 0.5 meters per second (1.1 mph) was used. The climatic data taken during 1975 at three plants averaged well over 5 mph.
2) No consideration was given to wind direction. This is very important since it can be presumed that any direction other than downwind will provide no detectable exposure.
3) No thermal buoyancy was used in the source stream. PVC plant drier outlets usually are above 140°F., and many other source points are mixed with live steam. These thermal gradients have a significant effect on effective stack height and mixing and, therefore, on the actual ground level concentration.
4) Average emission rates of 4.25% of the production of suspension plants were used and these emission rates are not representative of present day PVC & VCM operations.

The greatest deficiency in data prepared to support the proposed standard is the absence of an effort to correlate the actual monitoring results of 1975 with the model results, or to consider population distribution relative to prevailing winds. Analysis of the <u>downwind</u> data recorded by EPA at a Louisville, KY, plant provides an arithematic mean value less than 5 ppb at 1 mile compared to the predicted <u>average</u> value of 37 ppb on page A-3 of the Risk Assessment Document or less than 5% of the projections derived from the diffusion model. (Also see Table 4.1.2

STAR Document). Figure 1 is a plot of average measured concentrations from the 31 off-site downwind monitoring points at the Kentucky plant. Table I is a recalculation of the exposure for each area segment for which a population is given on page 1, multiplied by the rat lifetime risk calculated by Schneiderman (ANYAS 246 (1975) p. 239) to give an overall lifetime risk of <0.07 cases for 4.6MM persons, or <1.5 cases per 100MM lifetimes. Dividing by an average lifetime of 70 years and multiplying by 8 to adjust to 24-hour exposure this yields an annual risk of less than 2×10^{-9}, which is indistinguishable against the normal background of 0.128 per million for the general population, even assuming an equal sensitivity of rat and human.

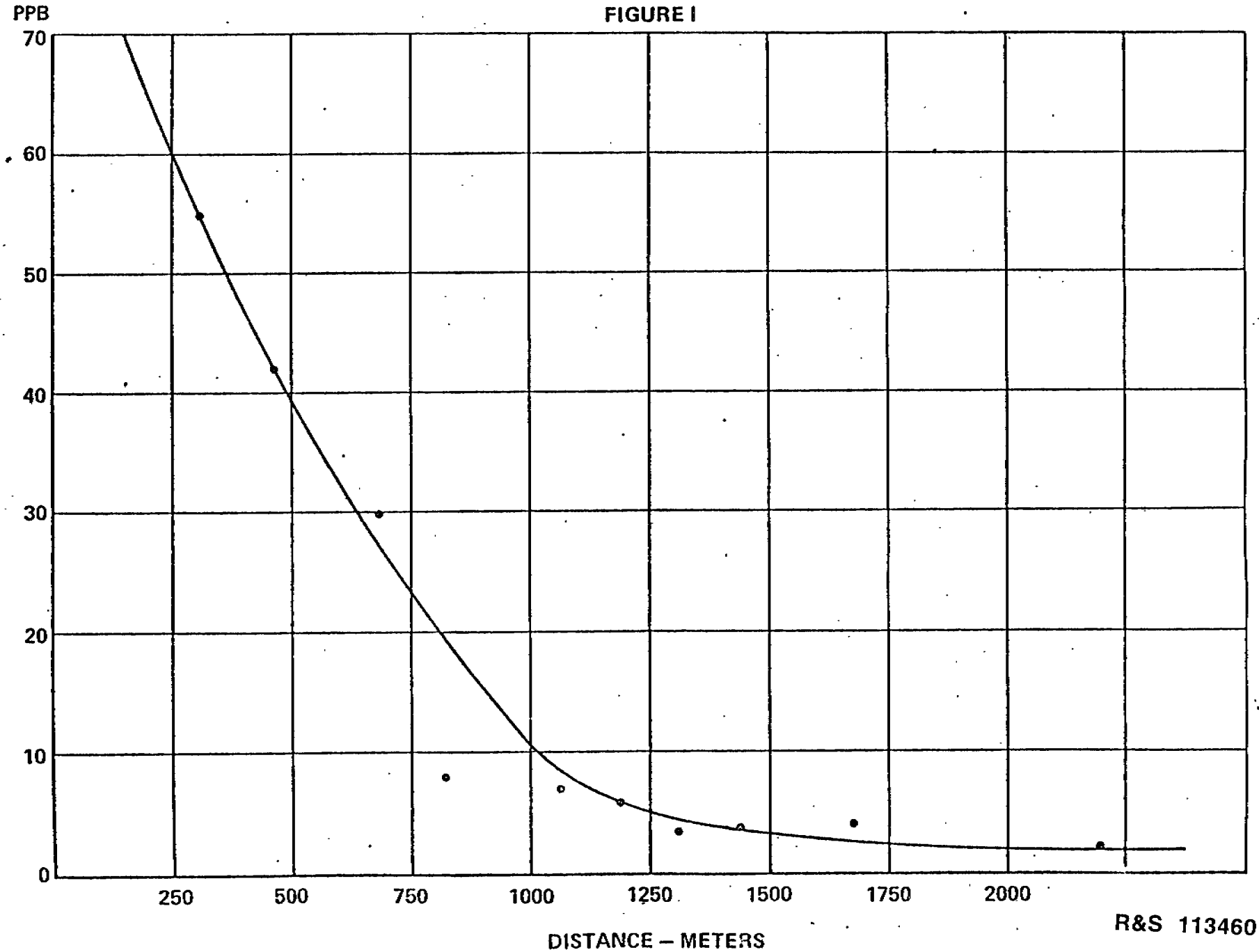
In view of these actual data, we find it difficult to understand how the authors of the Risk Assessment Document could use 17 ppb as the mean concentration of vinyl chloride for purposes of its predictions. Based on actual observations, concentrations are far less than this.

TABLE I

Area Segment	Population, Thousands	Average Concentration ppb	Risk	Total Lifetime Cases
$<1/2$ mile	47	45	5.4×10^{-7}	~ 0.03
1/2 - 1 mile	203	6	$<10^{-8}$	~ 0.002
1 - 3 miles	1,491	2	$<10^{-8}$	~ 0.01
3 - 5 miles*	2,838	<0.5	$<10^{-8}$	<0.03
	4,579			<0.072

*EPA has recognized that vinyl chloride deteriorates under conditions found in the ambient environment, yet it does not recognize the effect in the model. In addition, no EPA sampling data shows detectable vinyl chloride concentrations at beyond 3 miles from a PVC or VCM plant. The reduction in population exposed is obvious.

FIGURE I



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IV. Epidemiology

We also believe the Risk Assessment Document could have been more objective in presenting the epidemiological data. There are now 18 confirmed cases of angiosarcoma of the liver in the United States among persons occupationally exposed in high concentrations of vinyl chloride. None of the confirmed cases has occurred among persons involved exclusively in PVC fabrication or among persons whose exposure is only as a result of living in the vicinity of vinyl chloride production facilities. There are perhaps another 17 or 18 confirmed cases of liver angiosarcoma associated with exposure to vinyl chloride in the rest of the world.

Exposures to vinyl chloride among those who have developed hepatic angiosarcomas have been estimated because precise exposure data is unknown. All these estimates indicated that those who developed angiosarcoma had a very high exposure generally related to reactor cleaning. Reasonably precise exposure data are available for VC workers at the Dow Chemical Company plant at Midland, Michigan. None of these workers who had a lower exposure developed hepatic angiosarcoma.

The basic conclusion reached by the Risk Assessment Document on the epidemiological data is that "this survey has produced no evidence that living around vinyl chloride plants is a risk factor in the occurrence of liver angiosarcoma." (emphasis ours) However, the authors of the study then take great pains to minimize this conclusion. They suggest several reasons why the survey might have resulted in minimum findings, but do not discuss those reasons in sufficient detail.

The arguments the Document advances for not accepting its own conclusion are:

1) The latent time of 17 years means that the first exposure must have occurred prior to 1957 when the quantities of vinyl chloride produced were much less than current production.

Comment: This argument is only partially accurate. The angiosarcomas so far recorded in the United States show a latency period ranging from 12 to 32 years from known first exposure. In Great Britain one case has been reported with a latency of 9 years. (NIOSH Report 1975) Thus, using the U.S. minimum latency of 12 years, we are looking back to production in the year 1962 at the latest and perhaps even later. Vinyl chloride has been in production for 40 years. The atmospheric concentration for some plant sites could have been much higher than it is now although there is no way to retrospectively determine quantitatively how much community exposure occurred in the past. If we assume higher atmospheric exposures in the past than at present, fewer production facilities than exist now, and a latent period that is somewhat dose dependent we do not see that any conclusion can be arrived at other than that these factors may well balance each other.

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 living near a vinyl chloride plant.

Comment: Although it is not as true now as 40 years ago, workers tend to live near their place of work. Thus, there at least is as much likelihood that the 4.5 mile perimeter includes persons occupationally exposed as it does persons without any occupational exposure. We do not see any basis for saying that the risk is thereby underestimated. If anything the lack of occupational data should result in an overestimate of risk.

3) All existing liver angiosarcoma cases may not have been detected.

Comment: This is always true in any epidemiological study but hardly a basis to discount a survey unless there is some evidence that non-detected angiosarcomas exist in the exposed group.

4) The high percentage of cases having only residence at time of death obscures possible previous residence near a vinyl chloride plant.

Comment: The opposite situation is equally possible, that a person whose place of residence at the time of initiation of the tumor was not near a vinyl chloride facility and then moved near a production facility prior to death. There is no reason to believe that one situation is more likely than the other. We certainly agree that the residence at death does not necessarily indicate where most of the lifetime was spent.

5) A significant rate of change of diagnosis occurred when the cases on file were examined by pathologists at the National Cancer Institute.

Comment: This is not unusual with any type of tumor when the pathological specimens are submitted to a panel of pathologists who are specialists in the specific organ or tumor. In view of the low autopsy rate in the United States there is no way of insuring the accuracy of the incidence data for liver angiosarcoma and the number of changes in previously diagnosed cases could be more than balanced by cases that were never properly read by the pathologist and are therefore not included in the nationa figures.

All in all, the self-criticism by the authors themselves is unconvincing. The lack of risk based on present epidemiological data speaks for itself and may well throw into question the basis of the stringent proposed Standard.

V. Non-Carcinogenic Effects

In discussing the non-cancer effects of VC, the Risk Assessment Document does not discuss the possibility that VC may be a mutagen and/or a teratogen although this question has been raised in the scientific literature, the popular press, and suggested in the STAR Document. We recognize that research into the mutagenic/teratogenic effects, if any, of vinyl chloride is of recent origin and a number of defects exist in existing studie

Nevertheless, since the matter has received considerable publicity, it would be advisable for the document to discuss such studies as exist, if only to point out their limitations and the inability to draw any conclusions at the present time.

The only studies available on the effects on the fetus of community exposure to VC at the time the Risk Assessment Document was published was the report by Infante of an apparent increase in the incidence of birth defects in 3 Northern Ohio communities with nearby VC polymerization facilities. This study was reviewed and extended by the Center for Disease Control of the Public Health Service in a second study which reported that it could establish no relationship between the observed birth defects and VC exposure.

Any other concerns about community effects come from the extrapolation of work place exposures to the community exposures. Until very recently there has been only indirect evidence of any risk of genetically mediated disease as a result of VC exposures. This indirect evidence consisted of:

1. Evidence that VC is mutagenic in certain microbial test systems;

2. Indication of mutations in mammalian cells due to VC metabolites;

3. Demonstration in some studies that VC produces chromosomal changes in somatic cells in workers.

Direct evidence that VC may be mutagenic in man has become available only very recently in a report by Infante, et al. They report increased fetal wastage in wives of men occupationally exposed to VC in a polymerization plant where angiosarcoma of the liver has also been observed. We have two general comments about this study. First, it is related only to occupational exposures and has no direct relevance to vinyl chloride in the ambient air which is the focus of EPA's attention. Second, the study has several significant weaknesses as follows:[4/]

1. Limited size of population studies;
2. History obtained from husband rather than wife;
3. Data based on history only, no physician or hospital corroboration and no indication of age of wife;
4. VC exposure is not shown to be the only variable in the study;
5. No indication of incidence is given for the general population; it is not clear that rubber workers is the proper cohort for the comparison.

No human data are available with regard to any possible teratogenic effects of VC. Animal studies by Johns et al. show that VC is not teratogenic for rats, mice or rabbits either alone or administered in conjunction with ethanol.

4/ It also seems to be inconsistent with a December 1974 article, Chromosomen - Utersuchungen bei Vinyl Chlorid-Exposition, von I. Fleig and A. M. Thiess; Arbeitsmedizin, Sozialmedizin, Präventivmedizin 9,(12), pp. 280-283 (1974) which concludes that under the working conditions existing at BASF (Ludwigsh n, Germany) there was no evidence that the influence of VC had a mutagenic effect. We have been unable to trace the Norway Study to which Dr. Marcus referred at the hearing (Tr. p.73).

Conclusion & Recommendations

The most reasonable conclusion which can be drawn from the Risk Assessment Document and the other documents issued as part of the proposed Standard is that vinyl chloride poses no health risk for the general public because of the small concentrations which exist in the ambient air. Nevertheless, we believe a joint research effort should be developed because there are gaps in our knowledge of the health effects of the chemical at low doses.

An examination of the record demonstrates industry's participation in studying the health effects of vinyl chloride and in making these results public. Numerous scientific publications resulting from industry sponsored research can be found in the scientific literature beginning as early as 1961 and arrangements have been made to provide the government agencies with all reports of currently sponsored research. While there has unfortunately been at times a problem of maintaining a completely cooperative attitude, there must be increased efforts to arrange joint industry, labor, academic and government studies. There is serious need for cooperative studies to supplement and extend those already being sponsored and planned by the plastics industry through MCA coordinated and other research programs as well as those of government agencies. These studies should include:

1. Early detection and treatment of vinyl chloride induced injury. The University of Louisville has a major study under way in this area and the MCA Technical Panel on Vinyl Chloride Research is currently considering sponsoring additional work by this group. Additional studies by other groups may be desirable.

2. Metabolism studies. These studies need to be extended if we are to understand the mode of toxic action of vinyl chloride and its metabolites. Industry has sponsored most of the research in this area and expects to continue its efforts.

3. Mutagenic studies. Enough data are available to indicate concern for the potential mutagenic effects of high exposures to vinyl chloride. Likewise, available data indicate that low level exposures may not result in mutagenicity. It is obvious that research of the highest quality is needed to investigate and quantify the mutagenicity of vinyl chloride and to establish the practical hazard if one exists.

4. Human epidemiology. Perhaps no area requires joint effort as much as epidemiology particularly as related to cancer and birth defects. New methods of investigation must be developed and the resources of the government agencies must be properly directed to evaluate properly the effects of low levels of exposure on employees

and the public. Industry has been the leader in investigating worker populations, but the facilities and authority of the government must be used to study potential effects on the public health. These studies must be well designed, carefully conducted, objectively analyzed, and properly reported. "Quick and dirty" studies have no place in issues as important to society as management of vinyl chloride and its products.

We are not suggesting that government necessarily pay for the total cost of the studies which should be conducted. The burden should be shared by all interested parties. We do believe, however, that the government should take the lead in calling together interested parties with a view to establishing a consensus on what areas should be studied, who can best conduct the necessary studies, and the protocols which should be followed. The alternative, as we see it, is continued dispute over factual issues rather than concentrating on policy considerations which should flow from established scientific evidence.

RISK ASSESSMENT DOCUMENT

Executive Summary

Page	Paragraph	Line	Remarks
i	4	1-7	General Comment. Diffusion modeling methods, at best, offer only an approximation to the true state of affairs and can never substitute for actual monitoring data, which (although available) was unfortunately not taken into consideration. The weighting schemes proposed to account for the types, numbers and sizes of plants and the meteorological conditions are quite arbitrary, and different (but just as reasonable) choices for these weights would lead to a value much less than 17 ppb.
i	5	7	No cause and effect could be established by CDC Morbidity & Mortality, July 19, 1975, so the assumption should not have been made.
i	5	1-10	General Comment. Using animal data to predict human response is a very risky practice, because no real assessment of the validity of such an extrapolation has been made. The dose-response data for vinyl chloride is quite sparse (essentially only the Maltoni data is available), and no replications of such data are available for assessing the accuracy and precision of such data. The epidemiologic data available is of varying quality, and the Tabershaw-Gaffey data is the best data available and it was not used. There was considerable selectivity in the employment of information from these various studies, and the resulting conclusions drawn in this report are clearly unrepresentative of what the collection of studies taken together indicate.
i	6	1-5	General Comment. The assumption that a lifetime exposure to rats would produce the same number of effects as a lifetime exposure to humans has never been verified. The use of a linear model is certainly a very conservative procedure, but it does not provide as good a fit to the Maltoni data as a log-probit model (which is more often recommended when dealing with dose-response relationships of the type we are examining). The authors seem to have used the linear model more for convenience in computation than for its ability to accurately characterize the dose-response relationship. Indeed, there is no reason for preferring the linear model to the log-probit model, and, statistically speaking, the log-probit certainly provides a much better fit to the Maltoni data. The numbers in this paragraph certainly cannot be accepted at face value based on all the shaky assumptions used in arriving at them. Clearly, some consideration of the statistical variations surrounding these numbers should be made.

Page	Paragraph	Line	Remarks
ii	1	8	350 ppm is too low a dose. A much more appropriate dose would be that related to reactor cleaners over time period prior to 1974. Air Products' testimony at OSHA Hearing reports more realistic dosages in both U.S. and the United Kingdom. (STAR 6.1.4)
ii	2	6	"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 thus far been produced by vinyl chloride, only 38% of them have been diagnosed as of 1974." These are not facts but at best extrapolations from the models used in the study. The reasoning in arriving at the projection that 7.5% of all highly-exposed workers will get angiosarcoma is flawed. A correction factor is derived from the Tabershaw-Cooper Study and applied to the incidence date obtained by Nicholson. This is not appropriate since the hire dates in the Tabershaw-Cooper Study are a function of the starting dates of the plants in the T-C Study and not applicable to the single plant—Nicholson Study. If a correction factor is to be applied then the factor should be multiplied by the T-C rate so instead of 7.5% the percentage would be 1.2%; highly significant to the surviving workers.
ii	2	8	What is dosage for "highly-exposed workers" which relates to 7.5% expectancy of angiosarcoma?
ii	2	1-13	General comments. The probability 0.0031 (of a worker getting angiosarcoma at sometime in his life per year of exposure) is based on an incidence rate of 0.02, a value which is certainly <u>not</u> representative of the epidemiologic data as given (see, for example, the Tabershaw-Gaffey data, which are based on the largest sample size and provide the lowest incidence). No statistical measure of the error associated with this estimate is provided.

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Page	Paragraph	Line	Remarks
ii	3	1-3	General Comments. The fact that the probability estimate from the animal data (namely, .0052) is reasonably close to the estimate for the epidemiologic data (namely, .0031) says nothing about the accuracy of either of these estimates (i.e., two point estimates close to each other in value can be way off from the true value), and actually, in this case, only reflects the selective choice of what epidemiologic data to use to insure reasonable agreement with the animal data. There is no statistical basis for having much confidence in either of these numbers.
ii	5	1-12	General Comments. The fact that the better fitting log-probit model provides "low dose" (i.e., 17 ppb, which is too high) estimates of the number of cases per year of exposure which are 1/10 to 1/100 the size of those provided by the linear model casts serious doubt on the validity of extrapolation and on the use of the linear model itself. In addition, the use of a more reasonable and much smaller value than 17 ppb would considerably decrease these expected case values even more.
iii	1	5	"No conclusion can be drawn from the survey at its present stage of completion." This proposition is difficult to rationalize since the authors have already stated that their model predicts one excess liver angiosarcoma death with the 5-mile radius for each of the past 10 years. If we accept the actual number of cases projected to be found, i.e. (286/176 multiplied by 3) and add the upper bound of one excess angiosarcoma death per year for the past 10 years to the expected 5.9 from the Third National Cancer Survey we have an observed 4.9*vs. an expected 15.9. The probability of 5 or fewer cases with an expected of 15.9 based on the Poisson approximation is less than .002. If the expected were 13 the approximate probability would be .01. Is an observed of 5 (or less) reasonable in the light of an expected of 15.9? Any reasoned conclusion must be that the high values of risk resulting from the author's model are inconsistent with the upper end of model's risk. The survey begs a conclusion that the data does not support the upper spectrum of the modeled risk and is very consistent with no detectable risk.

...cont'd

*Case 3 has been confirmed as not being angiosarcoma. Therefore, only 2 unconfirmed cases remain in table 2 of Appendix E.

Page	Paragraph	Line	Remarks
cont'd			
iii	1	5	Another conclusion which should have been stated in the summary is that based on the CDC survey, "There is no evidence of clustering on a state-wide scale."
2	2	1-5	General Comments. The fact that the extrapolation from animal data to humans was based on assuming a (maximum) 168 hour exposure time per week (7x24) is certainly questionable in view of the remarks made in this paragraph regarding time spent away from home, etc.
2	3	4	General Comment. The statement that "the agreement between the two studies was good" does not say anything about the accuracy of either modeling approach. In fact, since both OAQPS and Teknekron used similar modeling procedures (except that the latter included data on meteorological conditions), they would be expected to provide reasonably comparable values. In this regard, the 25% discrepancy is somewhat high and reflects how much variation can be expected with such modeling procedures. It is regretable that the authors made no use of this 25% figure in studying the sensitivity of their predictions. Of course, the accuracy of such diffusion modeling is completely unknown and can only be assessed with actual monitoring data (which was not done in this report). EPA had such data (which strongly refutes the 17 ppb figure), but chose to ignore it.
3	2	1,2&3	"Unfortunately, it has not been possible to make a systematic comparison of the diffusion modeling results with data obtained from actual monitoring..." How can one talk about a risk assessment for community exposure to vinyl chloride without actually confirming the community exposure? EPA had monitoring data (STAR Series December 1975 pp. 29-30) which clearly shows the 17 ppb assumption not possible.
3	2	3-6	General Comment. Again, the authors refer to the difference of up to 25% between the two diffusion modeling efforts as an estimate of the uncertainty of these efforts, but do nothing to assess the effects of such uncertainty on their final conclusions. This is typical of much of this report--the final numbers coming out are (as the authors admit) greatly affected by such uncertainties, and no efforts have been made to assess the effects of such uncertainties.

Page	Paragraph	Line	Remarks
3	3	13-18	General Comment. The statement is made that "by using animal data, we can avoid such problems" (e.g., with regard to assessing health effects due to PVC and VCM exposures). However, the animal dose-response data is quite sparse and no replicate studies are available to assess the variation in such data, so that any conclusions are tenuous.
4	2	1-5	General Comment. "For technical reasons", the linear model was used instead of the log-probit to assess health effects. These reasons appear to be based on ease of computation and conservatism, etc., which are not sufficient justification for disregarding consideration of the better-fitting log-probit model, especially since no strong case for using only the linear model has been made.
4	5	1	"of the four occupational..." The Administrator should be advised of the epidemiology study on British Petroleum PVC workers published in Lancet, December 13, 1975, pg. 1197 to 1199, "Mortality Study of Workers in a Polyvinyl Chloride Production Plant."
4	5	12	"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." This estimate pertains only to highly exposed workers. An updated Tabershaw-Cooper report will issue before the Administrator promulgates a standard. This report will be the most complete study in the world. It will have greater than 95% follow-up; have a cohort size of 11,000 humans and will have 2,000 new records of a much older group of workers. Assumptions related to incidence of angiosarcoma and all cancers should be reviewed and revised based on this report.
4	5	14-15	General Comment. The issue of "competing risks" cannot legitimately be ignored, as it was; there are available statistical techniques for performing competing risks analyses, given adequate data.
5	2	2&3	In view of the admitted limitations of the Marsteller study which failed to compare exposed workers with a suitable control group, failed to consider the effect of alcohol intake and lacked exposure data, the alleged ratio should have been seriously qualified. In addition, under German law doctors are required to report "suspicions" of occupationally-related disease to insurance carriers as well as the government agency responsible for industrial hygiene. In this case, 70 cases of liver disease were reported without "findings stated"; they were apparently filed as a precaution.

Page	Paragraph	Line	Remarks
5	2	6,7&8	Allowance should have been made for the rat Zymbal Gland, which is an organ unique to rodents and particularly responsive to other chemical carcinogens (STAR 6.1.4). There is no way to extrapolate the incidence of neoplastic change in the organ in the rat to what might be expected in man. High local concentrations of chlorinated organic substances in the gland and the cellular characteristics of the organ are unique. There is consequently no valid basis for assigning an additional "non-angiosarcoma" tumor to man for each Zymbal Gland tumor. One must utilize organs and disease in which the conditions of exposure and response are fundamentally similar. Any use of the Zymbal Gland data for this purpose is inappropriate and misleading, primarily because of intense local exposure by lipid insoluble agents.
5	4	1-10	See exposure comments on Executive Summary, ii, paragraph 1, line 8. In addition, the data referred to was developed by Dow Chemical Co. records and is unlikely to be representative of the entire industry. It appears that, at least in some plants, exposure was much higher than indicated by the study.
6	1	8,9&10	The only real data to validate the modeling projections do not support and are not consistent with the linear model used in the study.
6	3	3	"1) The number of cancers at all sites caused by vinyl chloride is twice the number of liver angiosarcomas". There has been no "cause and effect" ever established; only associations and the cited data do not support the assertion.
6	3	3	"2) The number of people with severe liver damage is 30 times the number of liver angiosarcomas". Again this is not a result or fact but an assumption which should be clearly so stated.
7	2	1-8	General Comment. The authors "judge that the number of liver angiosarcomas produced per year of exposure in people residing near vinyl chloride plants is somewhere between less than one and 10 cases." This clearly has to be a very subjective statement, based on the fact that no proper statistical analyses were performed to accurately provide something like a confidence interval for the true number of cases. Also, there is no quantitative assessment of the validity of <u>any</u> of the assumptions leading up to these numbers, and so the numbers themselves are essentially meaningless. It goes without saying, then, that any manipulations involving these numbers (e.g., multiplying by 30) lead to just as questionable values.

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Page	Paragraph	Line	Remarks
7	4	6	"Unfortunately, the diagnosis of these cases has not yet been confirmed by the National Cancer Institute." It is difficult to understand why confirmation of 3 tissue specimens could not have been requested on a special basis for such an important document. The consequence of negative readings of these slides would suggest it is safer to live within 5 miles of a plant using VCM than outside that radius.
7	4	7	"In addition one infant whose parents lived within one mile of a plant died of a relatively common liver tumor." Since this is irrelevant, it is difficult to understand why the statement was included in the document?
7	5	4-7	The authors overlook the fact that PVC and VCM plants have been in operation in Niagara Falls for thirty years. There are no confirmed angiosarcoma cases in the vicinity of these plants. Upper New York State is similar to Connecticut in that a Tumor Registry is available. The Administrator should have been advised that the model would predict angiosarcoma cases in Niagara Falls or Louisville if it were valid. The facts show no cases in Niagara Falls after extensive epidemiology by CDC.
8	1	2-3	"If the lower rates in the range of the above analysis were to be true, increased incidence of angiosarcoma would not be observable." Can there be any other conclusion than that the facts do not support a model which predicts 10 cases per year?
Appendix A			
A-1	Last	0-1/2	Population of 47,000 is not correct because Texas City, Texas, population distribution should be in 1/2 to 1 mile annulus.

Page	Paragraph	Line	Remarks
A-2	3	1-2	"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." True, but the document should also have noted factors which will reduce the exposed population. Certain plants have or will shutdown and this will change population density gradient significantly. These plants are: 1) Hicksville, N.Y.; 2) Uniroyal at Painesville; 3) Carbide Dispersion Plant at South Carleston; 4) Goodyear at Niagara Falls reduced; and 5) Monsanto at Springfield, Mass.
A-3	4	Table of Data	This table completely overlooks EPA's own monitoring data and the reduction in VCM emissions brought about by OSHA compliance.
A-4	2	1-15	General Comment. The weights reflecting the meteorological conditions Low, Average, High and Very High are somewhat arbitrary and their values are subject to error. The way these weights were used in arriving at the 17 ppb figure means that it is very important to consider how much variability is associated with their specification.
A-4	3	16-27	General Comment. The weighting of a "large" PVC plant as being equivalent to 2.3 "average" PVC plants, because a "typical" large PVC plant has a production of 350 million lb/yr as opposed to a "typical" average PVC plant with 150 million lb/yr, is certainly an arbitrary procedure and has no statistical justification. A similar criticism for the weighting 1300/700 for "large" VCM plants can be made on the same grounds. The effects of different weighting schemes should have been examined.
A-5	1	10-11	"Since there are a total of 4.6 million people exposed within 5 miles of plants, the average exposure of these people is 76.4/4.6 or 17 ppb." Clearly EPA's own monitoring study cannot support the 17 ppb assumption. No discussion is offered to the Administrator of the impact of the OSHA standard on VCM emissions. In addition, the diffusion model includes solid and gas losses and does not take into account EPA's most recent monitoring data, see also comments on the technical standard, supra. The report deals with 17 ppb average community exposure in an absolute sense but the available data hardly support even 1 ppb. The implications of this difference in mathematics are critical to a rational decision by the Administrator.

Page	Paragraph	Line	Remarks
Appendix B			
B-1	1	9	"Ideally, we should use human data throughout and avoid the problem of extrapolating from an animal model to human beings." The Tabershaw-Cooper Study will be completed before the Administrator reaches his decision. (See previous comments) This data should be analyzed before the standard is finally promulgated.
B-2	2	1-5	Constraining the linear model so that it passes through the origin should be based on a priori rather than on a posteriori considerations. In fact, a slightly negative intercept is obtained without this constraint, and this suggests the possibility of a "threshold effect" (which could possibly be verified with further experimentation).
B-3	3	6	"Estimates of the total number of cancers caused by vinyl chloride are based on the slope of this line, not on the intercept." It would seem appropriate to comment on the special nature of the zymbal gland which is unique in rats.
B-3	4	1-2	The slope standard deviation estimates are only valid if the linear model is the correct one to use, and this is certainly open to debate.
B-3	5		The Maltoni animal data fits the log probit model better than the linear model, and there appears to be no reason why this should not be stated.
B-3	5	1-18	General Comment. The goodness-of-fit table looks impressive, but actually means very little because of the way in which the fitted model is eventually used. In particular, the fact that the linear model fits the data reasonably well in the region of experimentation means absolutely nothing with regard to extrapolation (i.e., prediction) outside the region of interest; in fact, a model can really perform well within the region of experimentation, but not be at all valid outside the region. Also, a similar table based on fitting the log-probit model would have indicated a much closer fit to the data, and, statistically speaking, the log-probit model would clearly be preferred on goodness-of-fit grounds alone.