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

SUPPLEMENTAL COMMENTS BY THE

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

On June 2, 1977, the Environmental Protection Agency (EPA) proposed amendments to the National Emission Standard for Vinyl Chloride (the "Vinyl Chloride Standard" or the "Standard")[1/] that was promulgated on October 21, 1976.[2/]

The Society of the Plastics Industry, Inc. ("SPI") has commented on many aspects of the proposed amendments. We will not restate or summarize those comments here. These supplemental comments will advise the Agency of an important new final report of an epidemiological study of vinyl chloride workers, and will respond to some of the claims made by the Environmental Defense Fund, Inc. ("EDF") in its comments on the proposed amendments. Because SPI's previous comments have discussed many of EDF's inaccurate contentions, these reply comments will focus on EDF's

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1/ 41 Fed. Reg. 46560-73 (1976).

2/ 41 Fed. Reg. 28154-59 (1977) (the "proposed amendments").

supplemental comments.[1] Additional comments on EDF's initial written comments[2] are set forth in Appendix I hereto.

I. The Epidemiological Study of Vinyl Chloride Workers by Equitable Environmental Health

SPI's previous comments focusing on the health-related issues raised by the proposed amendments reviewed the epidemiological evidence indicating that the adverse health effects alleged to result from vinyl chloride exposure have been observed only in workers with very high levels of exposure.[3] One study, published in 1974 by Tabershaw and Gaffey, examined the mortality history of 8,384 workers who had had at least one year of occupational exposure to vinyl chloride.[4] The study found no angiosarcomas of the liver in the lower exposure group.

Equitable Environmental Health, Inc. has prepared an expanded and updated final report based on the data used by

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1/ EDF (R. Rauch) letter to EPA (D. Goodwin), "Supplemental Comments to Proposed Amendments to the Final Emission Standard for Vinyl Chloride," dated October 4, 1977 (referred to as EDF's "supplemental comments" or "EDF Sup. Com.").

Although the deficiencies in EDF's suggestions are apparent from an examination of the article and study EDF has referred to, discussed in Section II, below, SPI is submitting these supplemental comments to assist the Agency in focusing on some of the incorrect conclusions EDF has suggested.

2/ "Comments of the Environmental Defense Fund on the Proposed Amendments to the Final Emission Standard for Vinyl Chloride," undated (referred to as EDF's "comments" or "EDF Com.").

3/ Comments by the Health Committee, PVC Safety Group, SPI, dated September 25, 1977.

4/ I. Tabershaw and W. Gaffey, Mortality Study of Workers in the Manufacture of Vinyl Chloride and its Polymers, 16 Journal of Occupational Medicine, pp. 509-18 (1974).

Tabershaw and Gaffey and additional data that later were located.[1/] That report examines the mortality history of 10,173 workers with at least one year of occupational exposure to vinyl chloride and analyzes the cause of death of 707 workers in the study population. The analysis examines the worker population and the identified deaths both by the duration of exposure and by the interval from the beginning of exposure to the end of the study. The Equitable Environmental Health Final Report was submitted to EPA on February 23, 1978.[2/]

Of the 10,173 workers in the study population, 9,677 (95.1%) were traced. Of the 707 known deaths, death certificates were obtained from state health departments for 669 (94.6%). (Equitable Rep. 6). Complete information was obtained for each individual in the study, including the history of exposure to vinyl chloride. All workers were classified by the estimated maximum level of vinyl chloride exposure to which they had been exposed for at least

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1/ Epidemiological Study of Vinyl Chloride Workers, Final Report, prepared by Equitable Environmental Health, Inc. for the Manufacturing Chemists Association, January 1978 (the "Equitable Report").

2/ Manufacturing Chemists Association (A.C. Clark) letter to the Honorable Douglas M. Costle, dated February 23, 1978. The basic data concerning the numbers and causes of deaths that occurred and were expected also were set forth in another Equitable Environmental Health epidemiologic study. Equitable Environmental Health, Inc., Epidemiologic Study of Vinyl Chloride Workers Employed by Union Carbide Corporation, South Charleston Plant, December 1976, at page 9, Table 1.

12 months. (Equitable Rep. 8).

> "Of the study population, 5,293 (54.7%) had had five or more years of exposure, 2,954 (30.5%) had had 10 or more years, 2,008 (20.8%) had had 15 or more years, and 1,001 (10.3%) had had 20 or more years exposure. Similarly, there was a large proportion in whom the interval from beginning of exposure had been long enough for delayed effects to be detected. In 5,484 (56.7%), 10 or more years had elapsed from the beginning of exposure until the end of the observation period; in 4,553 (47.0%) 15 or more years had elapsed; in 3,230 (33.4%) 20 or more years had elapsed; and in 1,705 (17.6%) 25 or more years of observation had been possible." (Equitable Rep. 7).

The vinyl chloride exposure of each worker in the study population was characterized in four different ways: (1) the duration of exposed employment, (2) the interval from the beginning of exposure to the end of observation, (3) the estimated maximum exposure over 12 months or more, and (4) the estimated integrated exposure. (Equitable Rep. 9). The mortality tables in the report show the numbers of observed and expected deaths and the calculated standardized mortality ratios for various combinations of the different exposure categories.

Since the report is available to EPA and the tables are lengthy, it will not need to be summarized here. The Equitable Report data, as well as the studies discussed in SPI's previous comments, do not indicate any need to lower EPA's existing Vinyl Chloride Standard.

II. <u>The Studies by Organization Resources Counselors</u>

EDF's supplemental comments discuss an epidemiological study conducted between March 1974 and December 1975 by Organization

Resources Counselors, Inc. ("ORC"). The data and findings were set forth and thoroughly discussed in a detailed, 52 page, February 1976 report entitled "Report on a Mortality Study Covering Employees of PVC Fabricators" (the "ORC Report").[1/] The same study also was discussed in a subsequent article by Drs. Chiazze, Nichols, and Wong, entitled "Mortality Among Employees of PVC Fabricators" (the "Chiazze article").[2/] SPI believes that EDF's supplemental comments reflect a fundamental misunderstanding of the ORC study, and quote and cite only selected portions of the study in a manner that may suggest unsupported and misleading conclusions.[3/]

The ORC study is "based upon 4,341 deaths which occurred during the period 1964-1973 among current and former employees of 17 companies engaged in PVC fabrication." (Chiazze art. 624). EDF has referred to the employees in the study population as "employees who were exposed to presumably much lower levels of vinyl chloride" than workers in vinyl chloride monomer and polymer

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1/ The ORC report was available to EPA and other interested parties well before the existing Vinyl Chloride Standard was promulgated and was referred to in the Agency record on which the existing Vinyl Chloride Standard was based. See reference 23 to Air Products and Chemicals, Inc. (R. Fleming) letter to EPA (D. Goodwin), dated Feb. 23, 1976, document no. D-36 in the Certified Index to the Record filed Feb. 17, 1977 in EDF v. Train, No. 76-2045 (D.C. Cir., dismissed June 27, 1977).

2/ L. Chiazze, W. Nichols & O. Wong, "Mortality Among Employees of PVC Fabricators." 19 Journal of Occupational Medicine 623-28 (Sept. 1977) ("Chiazze art."). Because the article discussed the same study and data set forth in the February 1976 ORC Report, EDF's reference to the study as "new information" is inaccurate. (See EDF Sup. Com. 1).

3/ Accordingly, these supplemental comments will contain quotations from the article and study that place EDF's quotations in the proper perspective.

production plants. (EDF Sup. Com. 3). EDF thereby apparently has implied that all the employees in the study were exposed to vinyl chloride. That implication is not true.

Whatever the employees in the study population had in common, it was not exposure to vinyl chloride. As discussed below, this fact is referred to in both the ORC Report and the subsequent article. A later ORC "Report on a Case Control Study Covering White Female Employees of PVC Fabricators," dated May, 1977 (the "ORC Case Control Study"), already submitted by SPI, further demonstrates that the workers in the study population had not all been exposed to vinyl chloride.[1/] In any event, even EDF has characterized the information and findings in the ORC study as only "potentially significant" (EDF Sup. Com. 1, 2), and has admitted that "the data is certainly not conclusive" (EDF Sup. Com. 3).

The methodology of the study is described in both the ORC Report and the Chiazze article. Several types of studies were considered. A mortality study was chosen because a "key factor" was "the urgency for completing the study within a limited time". (ORC Rep. 17). "[T]he scope of the proposed study was limited to employees of companies engaged in the fabrication of PVC resin into finished products". (Chiazze art. 623). The study population,

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1/ The case control study is Appendix III to "Comments by the Health Committee, Polyvinyl Chloride Safety Group, SPI", dated September 25, 1977 and submitted to EPA by SPI's (R. Harding) letter to EPA (D. Goodwin) dated September 27, 1977.

however, included all deaths of employees, both of workers exposed to vinyl chloride and workers not exposed to vinyl chloride.

> "A total of 55 plants supplied data on all identifiable deaths since, as was mentioned earlier, it was not possible to identify those employees with only vinyl chloride exposure for the study." (Chiazze art. 624).

This procedure was entirely appropriate because "[t]he primary objective of the study was to determine whether or not any angiosarcoma deaths had occurred among employees of the fabricators under study." (Chiazze art. 623), and only a limited time was available. It would have been a time consuming and impossible task to have reconstructed the work histories of the 4,341 deceased workers to see which had been exposed to vinyl chloride. Using all death certificates defined the largest maximum possible population. If an angiosarcoma of the liver had been found among the study population, that individual's work history then would have been reconstructed to see whether that employee had ever been exposed to vinyl chloride. (ORC Report 23).

The limitations of the study were recognized from the very beginning, and were expressly stated in the ORC Report. The Report recognized that all the study population had not even potentially been exposed to vinyl chloride.

> "Since the employee population was not homogenous as to numbers of employees in a plant, age, proportions potentially exposed to vinyl chloride gas, exposure to other possible toxic agents or mixtures of toxic agents, and residents in urban

> or rural areas, it was accepted at the outset that it might not be possible to draw firm conclusions at the completion of the study regarding the effect of vinyl chloride from the study population." (ORC Report 11).

Additionally, it was recognized that the study population would not be matched against a control group with the same characteristics. Thus, any apparent excess death rates suggested by the study could well have resulted from any number of causes, including substances to which all residents in particular areas might be exposed, such as drinking water contaminants or other air or water pollutants, or possibly other toxic agents.

> "Inasmuch as the fabrication of PVC resin into finished products is often a part of diversified product lines in a plant, and raw materials other than resin are utilized, employees may be exposed to toxic agents other than vinyl chloride. One of the problems in a study of this kind, therefore, is that it is not possible to isolate the effects of a single agent, such as vinyl chloride. Some of the variations from expected experience, reported in Chap. VI [Findings], may be due to exposure to vinyl chloride, or one or more other agents, or some combination." (ORC Report 10-11).

Moreover, the control group used was a non-industrial control group, while the study population consisted of industrial employees. This deficiency in the study is discussed in the comments on the ORC Report by Dr. G. M. Paddle, a noted statistician from Imperial Chemical Industries Ltd., that are set forth in Appendix II hereto.

Not only the ORC Report, but the Chiazze Article as well, pointed out that the data could not properly be interpreted as

indicating a cause-effect relationship between exposure to vinyl chloride and any apparent excess death rates.

> "[E]mployees may be exposed to toxic agents other than vinyl chloride. Consequently, in the current study, it is not possible to isolate only the effect of vinyl chloride."

Thus, the Chiazze Article itself continually emphasized the clear hazards in going beyond the limits of the data in suggesting possible conclusions. The article noted "several reasons why definitive interpretation is difficult", and expressly stated that "[f]actors such as these are meant to suggest that proportionate mortality analysis must be interpreted cautiously, with the intention of providing leads for future investigation." (Chiazze Art. 627). The clear limitations of the data in the ORC study were set forth even more clearly in the subsequent ORC Case Control Study. As originally planned, the mortality study to be performed by ORC was to consist of three separate steps. First, to "[s]elect workers whose deaths occurred during the 10-year period 1964-1973." Second, to "[e]xamine pathology for all cancer deaths plus all deaths from liver disease to verify whether or not any angiosarcoma deaths have occurred." Third, "[w]hen excesses occur, [to] obtain work histories for the employees concerned." (ORC Report 20). Even if all these steps were followed, it was known at the outset that "[a] mortality study is not as sound methodologically as a selected cohort study . . . ." (ORC Report 21). In any event,

each of the three steps were necessary to permit conclusions with respect to any relationship between the data and exposure to vinyl chloride.

As discussed above, including worker cases in the study regardless of whether the workers had been exposed to vinyl chloride was entirely acceptable because the maximum population would be included in determining whether there had been any angiosarcoma deaths. If no angiosarcomas were found, however, it is precisely because of this inclusion of all cases that the third step was necessary before conclusions could be drawn. In fact, steps one and two were accomplished and no angiocarcomas were found in the study population.

Due to that, the third step of identifying whether the workers in the study population actually were exposed to vinyl chloride, and on which conclusions could be based, was performed only on a part of the population of cases in the ORC study.

"In December 1976, Dr. Chiazze and ORC recommended that a case control study be conducted to determine the work histories of the white female employees in the study whose death certificates indicated breast cancer as the underlying cause of death. Only white females were studied, as no breast cancer deaths were found among males in the original study and the number of nonwhite females (23 deaths from all causes) was too small for further analysis" (ORC Case Control Study 4).

The case control study of the 44 breast cancer deaths was performed, including an examination and analysis of the work histories of the workers. As discussed below, the results demonstrate the total fallacy of presuming that all of the workers included in the initial, large ORC Study had been exposed to any vinyl chloride at all.

After the work histories had been obtained, the cases were classified by the worker's potential exposure to vinyl chloride into one of five categories: no exposure, improbable exposure, possible exposure, definite exposure, and unknown exposure. Of the 44 cases, 27 were found to have had "no exposure" to vinyl chloride. Another six were found to fall within the "improbable exposure" category. For one case, there was no record of the individual having worked in the plant. Four cases had "unknown exposure", and there was no information on another four cases. Only two of the 44 cases were classified as having had "definite exposure" to vinyl chloride.[1/] Thus, in the majority of the cases, the workers had not been exposed to vinyl chloride, and an even greater majority, 75 per cent, were found to have had either "no exposure" or only "improbable exposure".

Utilizing these vinyl chloride exposure histories, the case control study then subjected the data to statistical testing, and calculated risks to determine whether a relationship could be identified between the deaths and exposure to vinyl chloride.

1/ The numbers cited in the text are obtained by combining the exposure histories of the 35 cases with matched controls, set forth in Table 4 on page 21, with the exposure histories of the remaining nine cases, set forth on page 11 of the ORC Case Control Study.

No such relationship with vinyl chloride exposure was found in a Chi-Square test, even when the investigators used the assumption that all the cases with unknown exposure to vinyl chloride had been exposed and all the controls with unknown exposure had not been exposed, an assumption that "represent[ed] an extreme although highly unlikely possibility." (ORC Case Control Study 14-15).

The ORC Case Control Study demonstrates quite conclusively the limitations in the data from the larger ORC Study that were recognized from the outset and referred to both in the ORC Report and in the Chiazze Article. The 4,341 employees included in the population of the ORC Study were not all exposed to vinyl chloride, and therefore the data simply do not support or even suggest a conclusion that exposure to vinyl chloride had any relationship to the apparent excess proportionate mortality ratios.[1/] The study did determine unequivocally, of course, that no angiosarcoma deaths occurred among employees of the polyvinyl chloride fabricators under study. (Chiazze Art. 626-27).

The workers in the "low" exposure group in the Equitable Environmental Health study would have had a greater exposure to vinyl chloride than the workers in the polyvinyl chloride fabricating plants included in the ORC Study. The "low" exposure

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1/ It was beyond the purposes of the studies to speculate on whatever the cause of any excess proportionate mortality ratios might be. With respect to the 44 deaths studied in the ORC Case Control Study, however, the authors did find it "interesting to note that 40 of the 44 decedents worked in plants north of the Ohio River and east of the Mississippi River, where there is a deficiency of selenium in the soil." (ORC Case Control Study 5-6, footnote omitted).

group in the Equitable report, however, did not show any significant excess of cancer of any type. These results in the Equitable report clearly indicate that vinyl chloride exposures much higher than the small exposures that might have occurred in some of the workers in polyvinyl chloride fabricating plants included in the ORC Study have not caused the types of cancer that EDF's comments suggest were indicated by the Chiazze Article.

To further illustrate the misleading conclusions that would result from over interpretation and unwarranted extrapolation of the proportionate mortality ratio ("PMR") data in the ORC Report, information from the Equitable Study and the ORC Study have been combined in the table in Appendix III hereto so that the PMR's can be compared. The PRM's in the table must be considered as a range because an estimated 95% of the deaths were accounted for in the Equitable study, while less than 85% were accounted for in the ORC study. The table clearly indicates that for causes of death with sufficient numbers to draw an impression, the PMR's for the more highly exposed Equitable group are lower than those for the ORC group that was exposed to much less vinyl chloride, if any. Although it would be impossible to tell without additional case control studies whether any cause of death in the ORC study was excessive, if any cause were excessive it must be due to a factor other than vinyl chloride exposure or a similar pattern would have been observed in the Equitable group of vinyl chloride monomer and polyvinyl-chloride

production workers.[1/]

SPI's September 25, 1977 health-related comments also pointed out the existence of a substantial background incidence of angiosarcoma that is unrelated to vinyl chloride exposure. Several studies both in the United States and abroad have disclosed human angiosarcoma cases with no relationship to vinyl chloride exposure. EPA's own Risk Assessment Document recognized that the Agency's survey found fewer angiosarcoma cases near vinyl chloride production facilities than would be predicted on the basis of the national expected incidence of 20-25 cases per year.

Although we have not reviewed the Center for Disease Control's preliminary survey of angiosarcoma deaths referred to on pages 3 and 4 of EDF's Supplemental Comments, if the survey has been correctly represented, the CDC apparently found 225 to 250 cases of angiosarcoma during the eleven year period from 1964-74, or about 20 cases per year. EDF has claimed that only 10% of these cases have been linked to occupational vinyl chloride exposure, which would have been at high exposure levels. EDF further claimed that 10 additional cases were identified in 1975, 1976 and through October of 1977, or less than five cases per year. EDF's suggestion that unexplained angiosarcoma cases somehow possibly may be connected to vinyl chloride seems very doubtful indeed in light of this apparent decrease in cases. In light of the fact that the history of virtually every angiosarcoma case now is investigated

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1/ In addition to the studies discussed herein and in SPI's previous comments, the agency also should be aware of studies published in 59 J. Nat'l. Cancer Inst. 1383-85(1977) and in 2 British Medical Journal 919-21 (1977), and of the Health and Safety Executive's October 7, 1977 news release issued with the British study, captioned "Risk of Liver Cancer from VCM could have been overstated says report."

for possible vinyl chloride exposure, clearly there is no basis for concluding or even suggesting that totally unexplained angiosarcoma cases comprising the background incidence are related in any way to vinyl chloride exposure.

III. Risk Assessment

SPI has supported EPA's use of a risk-benefit-cost approach in developing the existing Vinyl Chloride Standard, and has not supported the zero emission goal concept suggested in the proposed amendments. The appropriateness of a risk-benefit-cost approach further is supported by the Administrator's "Proposed Federal radiation protection guidance" for persons exposed to transuranium elements. 42 Fed. Reg. 60956-59 (1977). In that proposal, the Agency utilized the criteria "that any added risk to an individual from exposure to the transuranium elements be very small, and that any actions required by implementation of the guidance be practical in terms of overall economic requirements." 42 Fed. Reg. 60957 (1977).

The Agency clearly recognized that radiation exposure to even very small amounts of radiation did have some finite risk to humans but nevertheless proposed to utilize a risk-benefit-cost approach.

> "[T]here is no level of radiation exposure which is absolutely safe and any radiation dose carries with it some degree of risk. Balanced against this is the fact that in our modern society all persons are exposed to a large number of competing risks (including natural background radiation) and that the reduction of a single risk must be viewed from the overall perspective of the costs and benefits." 42 Fed. Reg. 60957 (1977).

The use of the risk-benefit-cost approach is even more justified in the case of vinyl chloride exposure than in the case of radiation exposure because, as SPI has pointed out, there is substantial evidence of a practical threshold level of effects in man for vinyl chloride exposure.

IV. Non-carcinogenic effects

SPI already has submitted an independent evaluation and interpretation of available information relating to the possibility that vinyl chloride may be a mutagen or a teratogen.[1/] That report was prepared by Dr. Brian MacMahon, Professor and Chairman of the Department of Epidemiology of Harvard University's School of Public Health.

SPI has also obtained another independent evaluation and interpretation of such information by Drs. Thomas D. Downs, Revel A. Stallones, Ralph F. Frankowski and Darwin R. Labarthe.[2/] The authors of that review are all at the School of Public Health at the University of Texas' Health Science Center at Houston. They are, respectively, a Professor of Biometry, the Dean and Professor of Epidemiology, the Associate Dean and Professor of Biometry, and a Professor of Epidemiology. This report is included as Appendix IV to these supplemental comments, and offered as a comment on the proposed amendments.

V. Conclusion

SPI believes that the existing Vinyl Chloride Standard already provides an ample margin of safety to protect public health. We

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1/ See SPI Health Comments, pp. 16-17, and Appendix VI thereto.

2/ T. Downs, R. Stallones, R. Frankowski, and D. Labarthe, "Vinyl Chloride, Birth Defects and Fetal Wastage, a Critical Review," dated September 16, 1977.

know of no information that would indicate a need to lower the standard. Accordingly, the proposed amendments should be withdrawn.

March 9, 1978

R&S 113500

March 9, 1978

APPENDIX I

TO

SUPPLEMENTAL COMMENTS BY THE
POLYVINYL CHLORIDE SAFETY GROUP
THE SOCIETY OF THE PLASTICS INDUSTRY, INC.

This appendix will reply to some of the "Comments of the Environmental Defense Fund on the Proposed Amendments to the Final Emission Standard for Vinyl Chloride."1/

Page	Paragraph 2/	Lines	Remarks
1	2	1-3,9	SPI believes the existing Vinyl Chloride Standard meets applicable legal requirements and would have been upheld by the courts. See SPI's (R. Harding) letter to the Administrator dated November 22, 1977 and the memorandum submitted therewith. EDF has not provided any detailed support for its conclusion that the existing Vinyl Chloride Standard would have been overturned or remanded by the Court of Appeals.
2	2	3-6	EDF has not supported its conclusion that the revised limits in the proposed amendments can be met by improved operation of equipment being installed to meet the existing Standard. Compliance efforts to meet the limits in the existing Standard are underway under EPA-approved schedules. Because those limits have not yet been fully achieved, it is impossible to say that even lower limits could be attained with that equipment. See Statement of W.C. Holbrook for the Manufacturing Technology Committee, PVC Safety Group, SPI, dated July 19, 1977 (SPI's "Manufacturing Technology Comments"), pp. 4-6.

1/ These comments will not restate or summarize SPI's previous comments, although some cross references are provided.

2/ References to paragraph numb rs on a particular page include carry-over paragraphs. Carry-over paragraphs will be referred to as ¶1 on that page, and the first full paragraph on that page will be labeled ¶2.

Page	Paragraph	Lines	Remarks
2	2	6-7	The suggestion referred to, that industry reduce emissions to zero or shut down, was not adopted by the State of New Jersey.
2	3	1-5	SPI in fact was excluded from the settlement negotiations. EPA and EDF in fact did enter into a totally private agreement to propose amendments to the existing Vinyl Chloride Standard. In a meeting with Air Products and Chemicals, Inc., EPA's Deputy Administrator admitted that some of the proposals were "straw men." The proposed amendments did not reflect the considered judgment of the Agency, and EPA therefore failed to comply with applicable legal authority. EPA also failed to follow its own procedures and guidelines for proposing significant amendments to emission standards.
3	1	2-5	Because of the lack of definition of the proposed amendments and the lack of supportive data and information therefore, SPI's right to offer informed and thorough comments has been restricted. EPA has not yet answered SPI's requests in its August 19 letter to the Administrator.
3	1	5-7	EDF has cited no information to support its claim that it was excluded from meetings before the original Standard was promulgated. SPI and other interested parties did provide information and comments to EPA while the Agency was developing the existing Vinyl Chloride Standard, and some meetings between EPA and interested parties were held. SPI is not aware that EDF was ever excluded from any such meetings. Based on information available to SPI, EDF's charge is totally false.

Page	Paragraph	Lines	Remarks
3	1	10-13	The opportunity to file a petition for review in the Court of Appeals is not a substitute for proper administrative proceedings and responsible Agency action based upon adequate information.
3	2	1-3	The July 19, 1977 meeting was an "open meeting." No public hearing has yet been held on the proposed amendments.
4-7			EPA considered an enormous amount of information before promulgating the existing Vinyl Chloride Standard. A thorough and comprehensive record supported that Standard.
4	2	4-6	EDF's claim, that no data indicates any level of vinyl chloride exposure but zero is safe, is incorrect. SPI has pointed out that the epidemiological evidence is consistent with the existence of a practical threshold in man for exposures to low concentrations of vinyl chloride monomer. Many scientists have accepted the concept of threshold or no-effect levels for various substances. See Comments by the Health Committee, Polyvinyl Chloride Safety Group, SPI, dated September 25, 1977 (SPI's "Health Comments"). That position also has been strongly endorsed by Dr. Robert Olson. See Direct Testimony of Robert E. Olson, M.D., Ph.D., In Re Proposed Standard for Occupational Exposure to Benzene, OSHA Docket No. H-059, dated July 8, 1977.
4 5	3		In many respects EDF's comments are false or inaccurate, as demonstrated by SPI's Health Comments. In any event, this information was available to EPA before the existing Vinyl Chloride Standard was promulgated. To the extent it is significant it already is reflected in the existing Standard.
6	1		SPI has submitted an independent evaluation and interpretation by Dr. Brian MacMahon of available information relating to the possibility that vinyl chloride may be a mutagen or a teratogen. See SPI Health Comments, pp. 16-17, and Appendix VI thereto.

Page	Paragraph	Lines	Remarks
(cont'd)			SPI also has obtained another independent evaluation and interpretation of such information. It is included as Appendix II to these supplemental comments and offered as a comment on the proposed amendments. T. Downs, R. Stallones, R. Frankowski, and D. Labarthe, "Vinyl Chloride, Birth Defects and Fetal Wastage, A Critical Review," dated September 16, 1977. The authors of that review are all at the School of Public Health at the University of Texas' Health Science Center at Houston. They are, respectively, a Professor of Biometry, the Dean and Professor of Epidemiology, the Associate Dean and Professor of Biometry, and a Professor of Epidemiology.
7	1	5	EDF's statement that "Dr. Maltoni reported the induction of mammary carcinomas in rodents at levels of 1 ppm" is not true. Dr. Maltoni did not report that mammary carcinomas had been "induced" by 1 ppm vinyl chloride exposure. His report of the interim results stated that they had been "observed" and that in the breed of rats used "spontaneous incidence of mammary tumours show fluctuation from stock to stock of animals".
7	1	4, 8	Dr. Maltoni's interim data was available to EPA and actually was considered by the Agency before the existing Standard was promulgated. See SPI Health Comments, pp. 9-10.
7	1	9-13	To SPI's knowledge, no such "new data" concerning rodent tests in Bulgaria is available and EDF's claim is inaccurate. The cited memorandum does not support EDF's claim. It does not contain any data and does not set forth or discuss the tests, the methodology, the control group, or the results. The memorandum simply related a conversation with a NIOSH staff member in November, 1976 concerning experiments that had not then been concluded, and indicated the staff member would be given the results as soon as they were available. SPI is not aware that data has been provided or published. NIOSH did not provide any such data in responding to SPI's July 19 Freedom of Information Act request. The memorandum cited by EDF and its fragmentary hearsay information on interim results cannot serve as any basis for Agency action.

Page	Paragraph	Lines	Remarks
8-11			The proposed offset requirements have not been sufficiently defined by EPA to permit informed and thorough comments on the proposal. Some of EDF's comments are purely speculative and do not reflect the Agency's public explanations to date. Moreover, there is considerable question as to the Agency's authority to promulgate offset requirements for a particular chemical such as vinyl chloride under Section 112 of the Act. EPA chose to regulate vinyl chloride under Section 112 of the Clean Air Act and to promulgate a source emission standard.
8	1	7-10	Available evidence indicates that the existing Vinyl Chloride Standard provides an ample margin of safety to protect public health. EPA so determined when it promulgated the existing Standard. No evidence has been presented that would demonstrate a need to lower the existing Standard.
8	2		SPI agrees with EDF that the alternate approach mentioned, no growth, would have been unreasonable. SPI does not agree that such an approach could have been legally supported under Section 112 of the Clean Air Act.
8 9	3 1		The proposed offset requirements are not comparable to EPA's trade-off policy for new construction in nonattainment areas. The existing Vinyl Chloride Standard already requires each source subject to it to comply with specified emission levels. Available information does not indicate that the minute ambient vinyl chloride concentrations that may be present near a vinyl chloride plant pose any health threat. In fact, the evidence in the record indicates exactly the opposite. See the Dames and Moore report, enclosure 1 to SPI's (R. Harding) letter to EPA (D. Goodwin), dated August 19, 1977; SPI's Health Comments.

Page	Paragraph	Lines	Remarks
9	3	1	SPI does not agree that possible fugitive emissions from controlled plants constitute a major source of emissions.
10	3		See SPI's Manufacturing Technology Comments, pp. 21-22.
11	2		See SPI's remarks above, on p. 8, ¶3 of EDF's comments.
11	3	1-4	EDF's charge that "SPI has taken a fairly negative attitude about improving the level of vinyl chloride emitted from plants" is totally false. SPI and individual companies from the vinyl chloride industry provided a significant amount of information and data to EPA while the Agency was developing the existing Vinyl Chloride Standard. The vinyl chloride industry has commissioned and supported much of the research that has been accomplished to date into the health effects of vinyl chloride exposure. Although SPI had some reservations about the necessity for the stringent limits in the existing Vinyl Chloride Standard, SPI did not challenge the Standard but pledged the industry's best efforts to comply. The industry has met that pledge. When in compliance with the existing Standard, the industry will have achieved about a 95% reduction in vinyl chloride monomer emissions. The already low ambient levels of vinyl chloride will be drastically reduced by the existing Standard. Additional regulation is not necessary at this time. EPA should not finalize the proposed amendments.
12	1	7	Neither EPA nor EDF have provided estimates of the costs of complying with the proposed amendments. SPI has not been able to develop precise overall cost estimates of complying with the proposed amendments because the terms of the proposals have not been sufficiently defined by EPA. See SPI's remarks above, on p. 1, ¶2, lines 3-6 of EDF's comments.

Page	Paragraph	Lines	Remarks
13	1		SPI believes the existing Standard already provides an ample margin of safety to protect public health. EDF has totally ignored the fact that resources of the economy as a whole, of the vinyl chloride industry, and of individual companies are finite. Each dollar of resources spent to reduce the already infinitesimal ambient concentrations of vinyl chloride cannot also be spent for other productive uses, that could include additional research into the health effects of vinyl chloride exposure, and research into new control technology.
13	2		Precise calculations for the additional cost of building a new plant instead of expanding an existing one cannot be performed because the proposed amendments have not been adequately defined by EPA. SPI has offered a reasonable estimate. See SPI's Manufacturing Technology Comments, pp. 23-24. EDF has offered no estimate at all. EDF's comments totally ignore competitive concerns, and indicate EDF's complete willingness to accept increased consumer costs for vinyl products. The costs and other effects of the proposed offset requirements should be thoroughly studied before any such new requirements are adopted. The results then should be subject to appropriate cost-risk-benefit analysis. The lack of definition in the proposed amendments has prevented such study and analysis, and the proposed offset requirements should be dropped.
14 15	1		The FEA guidelines include energy efficiency goals for the chemical industry as a whole and also for specific subclasses. 42 Fed. Reg. 29642, 29661 (1977). The point of the targets is to promote increased energy efficiency, thereby decreasing energy usage. The proposed amendment to Section 61.62(b) is "based on installation of a recycling and oxygen feed system with an incinerator or equivalent control device." 42 Fed. Reg. 28155 (1977). The statement in the preamble that this technology would eliminate the supplemental fuel problem is incorrect. Energy would be required to generate oxygen for such a system and to incinerate the vent stream, but emissions would be reduced only by an insignificant amount. This increased

Page	Paragraph	Lines	Remarks
(cont'd)			energy usage cannot be justified. Moreover, EPA has no basis for the recycle/oxygen feed economics it assumed. SPI believes the existing Vinyl Chloride Standard provides ample protection of public health. See SPI's Manufacturing Technology Comments, pp. 13-14; Transcript of June 22, 1977 meeting at RTP.
15 16	3 1		SPI did not maintain inconsistent positions in its Manufacturing Technology Comments on the proposed amendments to sections 61.62 and 61.63, governing emissions from EDC purification and VCM formation and purification. Rather, SPI discussed EPA's documentation and demonstrated that EPA has not stated any rationale for proposing the 5 ppm emission limit in Section 61.62(b). SPI did not recognize emissions of 2.5 lb./hr. under the existing Standard, but noted that EPA's documents indicate that the maximum possible emissions would be 2.5 lb./hr. SPI did not suggest a 10 ppm limit on the oxychlorination process, but pointed out EPA's calculations showing the impact of various limits. See SPI's Manufacturing Technology Comments, pp. 7-9. No demonstrated basis or rationale exists for the proposed amendment to Section 61.62(b). It therefore should be dropped.
16 17	2 1		SPI requested Dames and Moore to conduct a diffusion modeling study because EPA did not conduct such a study before proposing the amendments to the existing Standard. The study's conclusions were highlighted in SPI's Manufacturing Technology Comments. Promptly after receiving Dames and Moore's report, SPI formally submitted three copies to EPA. See SPI (R. Harding) letter to EPA (D. Goodwin), dated August 19, 1977. SPI assumes that it was available thereafter to all interested parties, at EPA's Public Information Reference Unit. See 42 Fed. Reg. 28154 (1977).

Page	Paragraph	Lines	Remarks
(cont'd)			To our knowledge, EPA has not yet conducted diffusion modeling studies projecting the effect of the proposed amendments on ambient air concentrations of vinyl chloride. Nor has EPA conducted modeling studies of the effect of the existing Standard, beyond the inadequate studies on which the existing Standard was based. See SPI Health Comments, p. 7, and App. I thereto at pp. 8-11. EDF has submitted no diffusion modeling studies whatsoever, choosing instead merely to criticize the contributions of others. EDF's comments are incorrect in many respects. The Dames and Moore report certainly does not represent "best case" conditions as EDF has claimed. Indeed, it represents the opposite. Dames and Moore used EPA's numbers for unregulated emissions (EPA's interpretation of the May 1974, Section 114 data), for regulated emissions under the existing Standard, and for new plants in compliance with all of the proposed amendments. The numbers were used to model annual average concentrations in a realistic situation. The Houston meteorological conditions were used because they generally are considered "poor" and because other studies which have been made in this area can serve as reference data. The results were expressed as annual average concentrations because EPA selected and used that measure in its December 1975 Quantitative Risk Assessment for Community Exposure to Vinyl Chloride. The five-mile (8 km.) radius was used because EPA emphasized this distance in its risk assessment document and in the proposed offset requirements. EDF is wrong in suggesting the study predicted concentrations "at" five miles from a plant. The concentrations in the study clearly were stated to be those "within" a five-mile radius of the plant. Thus, distances closer than five miles have been considered. EDF also incorrectly speculates that a plant expansion "probably" would result in greater ambient levels than plant combinations. Emissions do not vary linearly with plant size, and some common equipment could be utilized in a plant expansion without added emissions.

Page	Paragraph	Lines	Remarks
(cont'd)			Although "worst case" conditions thus were used in the Dames and Moore study, the results clearly demonstrate that the proposed amendments, and particularly the proposed offset requirements, would not provide any meaningful change in already-infinitesimal ambient vinyl chloride concentrations. SPI believes the existing Standard already provides an ample margin of safety to protect public health. EDF has not provided evidence to the contrary.
17			The information cited by EDF was available to EPA before the existing Standard was promulgated. To the extent it is significant, it already is reflected in the existing Standard. Moreover, EDF's figures show the maximum at one given point. Points inside plant boundaries, of course, are not helpful in understanding possible exposure of residents. The figures cited by EDF do not show a violation of the OSHA rules. For specific comments on the figures cited, see App. I to SPI's Health Comments, pp. 8-11. In any event, actual monitoring has demonstrated actual concentrations far less than those predicted by EPA's model. The most reasonable course would be for EPA to withdraw the proposed amendments and, if desired, to check actual ambient concentrations after full compliance with the existing Standard has been achieved.
18 19	1		See SPI's remarks above, on p. 4, ¶2 of EDF's comments. EDF has not claimed that short-term exposure to the low ambient vinyl chloride levels does pose a health hazard, or even a health risk. Nor has EDF produced any evidence that could support such a claim. Rather, EDF simply has posed the question (p. 18, ¶1, lines 9-10), and then has discussed what it has characterized as "theories" and combinations of "theories." EDF has not defined the ambient levels or exposure durations to which it has referred. EDF's comments are pure speculation.

Page	Paragraph	Lines	Remarks
(cont'd)			Dr. Robert Olson, a Professor of Biochemistry and the Chairman and Professor of the Department of Medicine at St. Louis University's School of Medicine, has discussed dose-response relationships in the following terms:

> "The relationship between dose and response of an animal to vitamins, hormones, drugs, and a variety of biologically active compounds is never linear over a wide dose. . . . In biological responses there is always a 'no effect' level at the low end and a plateau at the high dose end of the curve."
>
> . . .
>
> "It is totally fallacious to extrapolate biological effects of drugs, toxins, nutrients, or hormones given at high dosage to low dosages. In the first instance, . . . biological dose-response curves are not linear on any coordinates over the whole range of possible dosage. Finally, there is in all cases, a low dosage at which there is no effect, at which a nutrient or hormone is biologically ineffective and a toxin is toxicologically insignificant."
>
> . . .
>
> "All drugs, and toxins demonstrate the threshold effect, i.e., a level at which the toxin becomes toxicologically insignificant."

Direct Testimony of Robert E. Olson, M.D., Ph.D., In Re Proposed Standard for Occupatoinal Exposure to Benzene, OSHA Docket No. H-059, dated July 8, 1977, pp. 9-11, 13. The entire testimony is instructive, and should be considered by EPA with respect to the proposed amendments.

Page	Paragraph	Lines	Remarks
19	1	3-4	EDF has not cited any evidence that the critical assumption mentioned in line 3, that "there are already carcinogens present which act in conjunction with the specific carcinogen under study", is warranted in the case of vinyl chloride.
19	2		The information on exposure to asbestos is not applicable to vinyl chloride. There is considerable evidence in the record that vinyl chloride is metabolized and does not accumulate.
20	1		Even as stated by EDF, its comments that a slight reduction in vinyl chloride levels "could" reduce the incidence of cancer are wholly speculative.
20 21	2		See SPI's Manufacturing Technology Comments, pp. 18-20.
21	1	2-4	EDF has provided no information to support its conclusion that a determination could be reached in the time allowed as to whether compliance with any proposed amendments could be achieved or an interim limit would be necessary. EDF has recognized the industry's superior technical expertise (p.22, ¶1, lines 6-7), and SPI has stated that that period of time would be totally inadequate to properly evaluate control systems being installed to comply with the existing Standard.
21	1	5-7	The proposed amendment to Section 61.72 provides no criteria whatsoever by which the Administrator would evaluate interim limit requests.
21	1	8-10	No adequate basis for EDF's assumption that "plant operators will have no difficulty obtaining such interim limits. . ." has been stated by EPA. It would be poor regulatory policy indeed to leave such matters to EDF's assumption.

Page	Paragraph	Lines	Remarks
21	2	1-2	Available information indicates that, at most, ambient vinyl chloride concentrations surrounding a plant would be very small. SPI believes the existing Standard provides an ample margin of safety to protect public health.
21	2	6-8	SPI agrees that confidential and proprietary information should not be disclosed, but the proposed amendments do not so specify. SPI also is concerned that information might be disclosed inadvertently. EPA has recognized industry's concern that "there might not be adequate safeguards within EPA to protect against disclosure of confidential business information." 42 Fed. Reg. 57984 (1977) (Re: TSCA Data Security Task Force).
21	2	10-15	EDF has not suggested any mechanism for a meaningful public meeting while protecting from disclosure the confidential and proprietary information. Any person or company, of course, already may forward any information on control technology to EPA, to industry groups, or to individual companies.
22	1		See SPI's remarks above, on p. 11, ¶3, lines 1-4 of EDF's comments. Zero emissions is unattainable without a complete shut down of the vinyl chloride industry, which was not intended by Congress. See Statement of Ralph L. Harding, Jr., President, SPI, dated July 19, 1977, p. 10, ¶¶3, 4; SPI's (R. Harding) letter to the Administrator dated November 22, 1977 and the memorandum submitted therewith.
23	2	2-3	EDF's Comments are inconsistent. E.G., compare with p. 22, ¶2, line 13.
22 23	2		SPI believes the existing Vinyl Chloride Standard sets an ample margin of safety to protect public health. For reasons stated above and in SPI's other comments, the proposed amendments should be withdrawn.

APPENDIX II

TO

SUPPLEMENTAL COMMENTS BY THE
POLYVINYL CHLORIDE SAFETY GROUP
THE SOCIETY OF THE PLASTICS INDUSTRY, INC.

COMMENTS BY DR. G. M. PADDLE ON THE ORC REPORT[1/]

"I would like to put on record a few remarks about the above paper. The key Table is Table 6 on page 43, which is as remarkable for what it omits as for what it includes. It is a Table of deaths due to 'selected causes', and as such reflects the attitudes of the person responsible for the selection process. The summary statistic is the PMR which, though a sensible choice in this instance, cannot be considered in isolation from the number of cases involved. I have revised this Table overleaf, adding the statistic (Observed - Expected) (Square root of Expected), for which values of ± 2 can be used for significance testing, and adding two other miscellaneous cause groups. It is a common feature of studies of industrial employees that there is a reduced frequency of deaths from miscellaneous causes, which is compensated for, on a proportional basis, by an increase in the numbers of cancer cases. This feature is apparent in the revised Table for males. There is a highly significant deficiency of deaths from 'all other' causes and a significant excess of cases of 'other cancer' as well as digestive and respiratory cancer. In addition, the apparently innocuous PMR of 1.05 for circulatory disease is shown to be significant. In other words, an explanation in terms of a lack of those diseases which debar employment is as valid as an explanation in terms of those diseases 'caused' by employment. Analyses of female employees are less common, so that argument by analogy is less satisfactory. The figure for 'other cancer' suggests that the figures for digestive and breast cancer are part of a general transfer to cancer. That the transfer is from circulatory diseases rather than from 'all other' diseases is somewhat unexpected."

"In summary, I feel that the results are a restatement of 'the problem of employees in industry' rather than a reflection of particularly adverse conditions for PVC fabricators."

1/ Memorandum of Dr. G. M. Paddle, Imperial Chemical Industries, Ltd., dated July 13, 1977 and captioned "Report on a Mortality Study Covering Employees of PVC Fabricators."

APPENDIX III

TO

SUPPLEMENTAL COMMENTS BY THE
POLYVINYL CHLORIDE SAFETY GROUP
THE SOCIETY OF THE PLASTICS INDUSTRY, INC.

COMPARATIVE ANALYSIS OF MCA AND ORC STUDIES

Cause of Death with ICD Number[b]	MCA Study Total VC-PVC Workers Obs./Exp.	SMR[a]	PMR	ORC Study Total Fabricators Obs./Exp.	PMR
All causes	707/795.02	88.9**	0.95-1.00		0.85-1.00
All malignancies (140-205)	139/141.39	103.9	1.05-1.10	665/562.8	1.00-1.18
Malignant neoplasms, buccal and pharynx (140-148)	5/ 5.19	101.8	1.03-1.08	15/16.9	0.76-0.89
Malignant neoplasms, digestive organs and peritoneum (150-159)	29/ 40.82	75.1	0.86-0.90	210/162.3	1.10-1.29
Malignant neoplasms, respiratory system (160-164)	45/ 44.29	107.4	0.89-0.94	205/176.9	0.99-1.16
Malignant neoplasms, genital organs (170-179)	4/ 7.17	59.0	0.60-0.63	42/58.0	0.61-0.72
Malignant neoplasms, urinary organs (180-181)	8/ 6.85	123.4	1.26-1.33	36/33.2	0.93-1.09
Malignant neoplasms, other and unspecified sites	28/ 20.18	146.6			
Leukemia and aleukemia (204)	9/ 6.65	143.1	1.90-2.00	61/55.8	0.93-1.09
Lymphomas (200-203, 205)	11/ 10.36	112.3	1.17-1.23		
Major cardiovascular and renal diseases (330-334, 400-468, 592-594)	347/385.24	95.2	1.09-1.15	1933/1835	0.89-1.05
Cirrhosis of liver (581)	14/ 26.45	55.9**	0.56-0.59	42/162.9	0.57-0.67
All other certified causes	169/241.95	73.8**	0.74-0.78	568/740.7	0.65-0.77
Number of workers	9,677				
Number of person-years	120,203				
Number found	0.951			0.85	

a [redacted]s adjusted for deaths with unknown cause.
b Numbers indicate categories in the 1955 version of t[redacted] International Classification of Diseases.
* Significant at the 0.05 level.

APPENDIX IV

TO

SUPPLEMENTAL COMMENTS BY THE
POLYVINYL CHLORIDE SAFETY GROUP
THE SOCIETY OF THE PLASTICS INDUSTRY, INC.

VINYL CHLORIDE, BIRTH DEFECTS, AND FETAL WASTAGE

A CRITICAL REVIEW

by

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Prepared for

The Society of Plastic Industries, Inc.

by

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September 16, 1977

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1. History and Background

Vinyl chloride is a gas under normal pressures and temperatures. It was found to produce cancers in some of a group of rats exposed over a period of time to a vinyl chloride ambient air concentration of 30,000 parts per million (30,000 ppm) by Viola in 1971 [1]. Maltoni, reporting in 1975 [2] on experiments begun in 1971, showed that 9 of 61 rats exposed to a concentration of 10,000 ppm intermittently for one year developed liver angiosarcoma. Since liver angiosarcoma is extremely rare in both mice and men [3], this was considered overwhelming evidence that vinyl chloride was the cause of the liver angiosarcoma.

In December of 1973, before Maltoni published his results, the B.F. Goodrich Chemical Company discovered two cases of liver angiosarcoma and a suspected third case in workers in a Louisville, Kentucky vinyl chloride plant, and reported this the following month to the Director of the United States National Institute for Occupational Safety and Health (NIOSH) [4]. Since liver angiosarcoma is such a rare disease, it was suspected that these cases may have been related to occupational exposure to vinyl chloride. The experiments then being conducted in Italy by Maltoni took on a new urgency, and the United States Environmental Protection Agency (EPA) initiated several actions.

The following excerpts from the Federal Register [5] illustrate the position and some of the actions of the EPA with regard to the above vinyl chloride issues:

> EPA established a Task Force on vinyl chloride in February 1974, to identify the environmental problems resulting from the manufacture and use of vinyl chloride and polyvinyl chloride. While air, water, and solid waste disposal are all possible routes for entry of vinyl chloride into the environment in the vicinity of manufacturing facilities, the Task Force concluded that, based upon current information, the air route poses the most significant environmental problem to the population located there.
>
> Any substance which is shown conclusively to cause tumors in animals should be considered carcinogenic and therefore a potential cancer hazard for men.
>
> However, an emission standard for vinyl chloride cannot be established below a threshold level of effects because no dose-response data are available for the concentrations of vinyl chloride found in the ambient air.
>
> No level of exposure to a chemical carcinogen should be considered toxicologically insignificant for man. For carcinogenic agents a safe level for man cannot

be established by application of our present knowledge. The concept of 'socially acceptable risk' represents a more realistic notion.

Because the latent period in human carcinogenesis is so long, epidemiologic evidence develops only over periods of 15 to 20 years. Timely decisions to exclude materials from uses involving exposure to man, therefore, must be based solely on adequately conducted animal bioassays.

A concurrent issue before EPA was what level of emission control could or should be required under section 112. Section 112 provides that the Administrator shall set an emission standard 'as the level which in his judgment provides an ample margin of safety to protect the public health from such hazardous air pollutants.'

Further, it is EPA's position that for a carcinogen it should be assumed, in the absence of strong evidence to the contrary, that there is no atmospheric concentration that poses absolutely no public health risk. The issue was how far the level of such pollutants should be reduced to provide 'an ample margin of safety.'

Complete prohibition of all emissions could require closure of an entire industry. This would occur in a case such as vinyl chloride where there is no technology to achieve a zero emission limitation and development of such technology is not foreseen. Closure would result in extensive economic costs in some cases, such as when the affected industry is of large size or there are no available substitutes for the products produced. The costs of a prohibition in some cases would be extremely high for elimination of a risk to health that is of unknown dimensions.

In view of the beneficial uses of vinyl chloride products for which desirable substitutes are not readily available, the potentially adverse health and environmental impacts from substitutes which have not been thoroughly studied, the number of employees particularly in fabrication industries, who would become at least temporarily unemployed, and the availability of control technology which is capable of substantially reducing emissions of vinyl chloride into the atmosphere, EPA concluded that setting zero emission limits would be neither desirable nor necessary.

The United States Occupational Safety and Health Administration (OSHA) imposed stricter standards for workers exposed to vinyl chloride. The EPA adopted tighter air-emission standards for vinyl chloride plants, so as to reduce community exposure to vinyl chloride. And a number of epidemiologic studies on potentially hazardous effects of vinyl chloride were begun. This review deals with such of these studies as involve a possible association between vinyl chloride and human birth defects. Such studies as have been published can be classed into the following areas:

(A) possible chromosome aberrations in workers exposed to vinyl chloride,

(B) possible excess wastage in fetal offspring of male vinyl chloride workers,

(C) possible excess birth defects in communities with PVC production facilities.

Reviews and critiques of the literature relating to these three areas appear in the next three sections, and these are limited, necessarily, to published studies only. Our critiques consist of analyzing the individual studies within an area, and synthesizing the several studies in each area to arrive at an overall conclusion therein, as best we can determine from the available scientific evidence. Our own conclusions are necessarily judgmental in large part, and based on such elements as estimates of the competency and training of the investigators, freedom from bias, study scope and design, adequacy of facilities and resources, adequacy of control groups, and adequacy of statistical analyses. For synthesizing the several studies in an area it will be noted that each of the above three areas may be considered as an hypothesis stating an association of vinyl chloride with the area, so the consistency, strength, specificity, temporal pattern and coherence of this association is judged for each study, and the results synthesized with the individual studies weighted according to our assessment of the validity of their conclusions.

Our recommendations and a summary of our conclusions appear in the last section.

2. Chromosome Aberrations

The evidence is overwhelming that vinyl chloride is, in sufficient doses, carcinogenic to animals and to man. Since carcinogenic chemicals are often mutagenic [6], a study was undertaken in Sweden in 1975 by Funes-Craviato et al. [7] to determine if there were excess chromosome aberrations in vinyl chloride workers. This study was funded jointly by the Swedish Medical Research Council and the Swedish Board of Occupational Safety and Health. The sample consisted of seven exposed male workers and three non-exposed controls. Durations of exposure to V.C. ranged from 9 to 29 years for those in the exposed group. The number of cells analyzed per subject ranged from 150 to 250. Chromosomal analyses were made on lymphocyte

cultures incubated for 48 and 72 hours. All blood specimens were coded and analyzed blindly. The authors state that data for the three control subjects were homogeneous, and these data were therefore pooled. On the other hand, for the exposed group, the highest frequency of abnormal cells was found in those subjects who had the shortest duration of exposure. Further, a χ^2 test for the seven exposed workers showed significant deviation from homogeneity ($P < 0.001$), and two of the exposed workers (with 12 and 20 years of exposure) did not differ significantly from the controls. Nevertheless, the seven exposed worker data were pooled, and the frequency of abnormal cells (9.5 percent) in the exposed group was found to be significantly greater than the frequency (1.9 percent) for the controls with a stated P value less than 0.001.

No information is given on how the three control subjects were selected other than that they were "non-exposed" and worked in the same factory as the seven exposed workers. Individual chromosome aberrations are not given, either, for the three controls, but instead totals are presented. In a study such as this we, ideally, would like to have the control group, as a group, similar in as many relevant respects as is feasible to the exposed group, so that any difference in chromosome aberrations between the two groups can reasonably be attributed to the exposure, and only to the exposure. It is not possible to attribute the difference, 9.5 percent versus 1.9 percent, in this study to exposure to V.C., because very little is known about the control group. The authors state that,

> . . . The frequency of aberrations [in the control group] nevertheless accorded with that of a male population selected at random.

But this in itself does not correct the situation. Suppose, as an extreme example, that all three controls were x-ray technicians and that laboratory techniques on all ten subjects were such that all results were biased downwards. Then the situation would actually be worse than the 9.5 percent versus 1.9 percent stated. Conversely, the seven exposed workers were exposed from durations of 9 to 29 years, so their age range is from perhaps 30, to at least 50. Then, if the exposed workers have had periodic chest x-rays, and the control group is younger and so have not, the situation would be better than as stated.

There are seven exposed, and three control, subjects in the study, with totals of 1450 and 566 cells examined in the two groups. The sample sizes are 7 and 3, and <u>not</u> 1450 and 566, since cells come in clusters in the subjects. Any chi-square tests on cell counts tacitly assume sample sizes of 1450 and/or 566, and are therefore invalid (see pp. 513-15 of Statistical Methods, 6th Ed., by Snedecor and Cochran [8]). The appropriate statistical test to compare the average aberration frequencies in the two groups is the two-sample t-test, with standard deviations computed as in [8, p. 515]. It is not possible in this instance to compute exactly the t statistic since the individual cell counts and aberrations for the three controls are unknown, so that no standard deviation can be obtained for this group. As an extreme case let us suppose this latter standard deviation is zero. The

standard error of the mean, 9.5 percent, for the exposed group is found [8, p. 515] to be 2.2, so that t is at most (9.52 - 1.94)/2.2 = 3.44, with 6 degrees of freedom. Then $0.01 < p < 0.025$ under this extreme assumption of zero standard deviation, in marked contrast to the statement by the authors that $p < 0.001$. A more realistic assumption about the standard deviation of the control mean would render the difference, 9.5 - 1.9, non-significant at the 5 or even the 10 percent level. Even so, the interpretation of such p values is fraught with indecisiveness by virtue of the design defects brought out in the preceding paragraph.

A second and similar blind study, also published in 1975, was carried out by Ducatman et al. [9] in the United States at the Mount Sinai School of Medicine of the City University of New York. There were eleven exposed male workers and ten "healthy male controls" in this study. Four of the ten controls worked in the same factory as the exposed workers, but were "without known vinyl chloride exposure." The other six were selected "older controls outside the factory environment." Still, the average age of the controls was only 27, while that of the exposed group was 40. Fifty lymphocyte cells from each of the 21 subjects in the study were examined. In this, as in the previous study, levels of exposure and total amounts of exposure are unknown:

> Duration of recurrent occupational exposure in the 11 men ranged from 4-28 years with an average of 15 years. . . . There is no record of ambient gas levels in the factory, but it is assumed that these must have exceeded 500 ppm at times, based on reports of odor detection, dizziness, and headaches.

The methods used to select exposed and control subjects for this study were not stated.

Confirmed aberrations in this study were classified according to two systems in order to discern if a pattern of breakage might exist. The system of Buckton et al. [10] has three categories of aberrations: B for breaks and gaps, C_u for unstable changes, and C_s for stable changes. The number of aberrations in each of these three categories is presented for each of the 21 subjects. Also presented are the ages of each of the 21 subjects and the duration of exposure of each of the 11 exposed workers. Hypotheses tests were done via the appropriate t-test, in contrast to the previous study which used the inappropriate χ^2-test. The results are summarized here:

Category	Exposed		Control		t	p
	Mean	St. Dev.	Mean	St. Dev.		
B	5.64	1.91	4.40	0.97	1.84	< 0.10
C_u	1.55	1.29	0.30	0.48	2.86	< 0.01
C_s	3.36	1.63	2.90	2.18	0.56	< 0.60

The means are averages of aberration counts. The difference in means for the C_u category is just significant at the 1 percent level--the differences for the other two categories are not significant (at the 5 percent level). The average percentages of chromosome aberrations total 21.1 percent for the exposed group and 15.2 percent for the control group. These results are incompatible with those of the previous study wherein the percentages were 9.5 and 1.9, respectively.

The second system used to classify aberrations in this study is due to Hirschhorn and Cohen [11]. This system considers breakages only and classifies them as S (simple or "single hit") or C (complex or "double hit"). The total number of breaks per individual is calculated as S + 2C. A summary of the results is given in the following table:

Category	Exposed		Control		t	p
	Mean	St. Dev.	Mean	St. Dev.		
S	1.91	1.44	1.30	0.95	1.12	< 0.30
C	2.00	1.67	0.40	0.70	2.80	< 0.02
S + 2C	5.91	3.91	2.10	2.02	2.75	< 0.02

The comparison for the S category is not statistically significant, but the other two comparisons are. However, the problem is how to interpret the significant P values. By crafty selection of a control group one could make a study come out any way one pleases. In our judgment it is the responsibility of the investigator, asserting a statistically significant association, to furnish evidence that the association is due to the factor under test (in this case exposure to V.C.), and not due to other extraneous factors. Such evidence should include the methods whereby subjects are selected for the treatment and for the control groups.

In the previous study no association was found between frequency of aberrations and duration of exposure. This phenomenon recurs in the present study. For instance, the worker with the largest total number of breaks (S + 2C) in the exposed group had the shortest duration of exposure (13 breaks, 4 years), while the worker with the smallest number of breaks (0 breaks) had 17 years of exposure. In the discussion section the authors state that,

> There are obvious perils in drawing strong conclusions from small samples, and it would clearly be preferable to have an age-matched control group despite experimental evidence that age is generally unrelated to chromosome changes other than chromosome loss. Also, the relatively high degree of breaks and gaps in controls as well as subjects is somewhat disconcerting, although subjects do have more.

and next state that,

> Within these limitations, it is clearly indicated that chronic high level exposure to vinyl chloride is clastogenic.

We have had difficulty in interpreting this conclusion.

A third study on chromosomal effects of vinyl chloride on V.C. workers, also blind, and also published in 1975, was done by Purchase et al. [12] in England under the auspices of Imperial Chemical Industries, Limited. They state,

> We have studied 80 workers, 56 of whom had been working in the manufacture of P.V.C., and were thus exposed to V.C.M.: the remainder were working in plants and laboratories where exposures to V.C.M. did not occur. The exposed group consisted of autoclave workers, maintenance workers, and workers associated with the manufacture of vinyl chloride. Blood samples were taken and lymphocyte cultures prepared using standard Difco Kits (Difco Laboratories, Detroit, Michigan, U.S.A.). Lymphocytes were cultured for 48 or 72 hours. All slides were coded before scoring to ensure unbiased analyses, and 100 cells from each individual were analyzed using the classification of Buckton and Pike. Workers who had been exposed to x-rays, prolonged drug treatment, or recent viral infections were excluded from the study.
>
> The results from 48 and 72 hour cultures were not significantly different and these data have been pooled. The results are given in the accompanying table [reproduced below] where it can be seen that there is a significantly increased ($P < 0.05$) percentage of B, C_u, and C_s cells in the exposed workers. These results, which confirm those of the previous authors [7,9], suggest that vinyl chloride has a detectable effect on chromosomal aberrations in man.

Chromosomal Aberrations in Vinyl-Chloride-Exposed Workers and Controls Not Exposed to Vinyl Chloride

Exposure Category	No.	Percent B Cells	Percent C_u Cells	Percent C_s Cells
Exposed	56	6.30	1.45	0.38
Non-exposed	24	3.63	0.46	0.09

The above constitutes the totality of information given on this study. It is not clear what statistical methods were used to test hypotheses. The methods used to select subjects for the control group were not stated. No information is given on exposure durations, nor on the ages of the subjects. No reasons are given as to why the differences in chromosome aberrations between the two groups could not be attributed to some factor other than vinyl chloride.

Each of the above three studies deals with a possible association between vinyl chloride and chromosome aberrations. We have attempted below to synthesize these studies accordingly.

The statistical methods used were inappropriate in the first study, appropriate and clear in the second, and unspecified in the last study. None of the three studies contained a description of any sort on how the control group subjects were selected, and only one of the studies gave any ancillary demographic information on the control group. The first two studies showed no positive association between duration of exposure and frequency of abnormal cells--in fact the associations seemed to be negative in both cases, though not statistically significant. The third study gave no data at all on exposure durations. The average percentages of abnormal cells in the exposed groups ranged, over the three studies, from 8.1 percent to 21.1 percent, and for the control groups from 1.9 percent to 15.2 percent.

On the other hand, the results of all three studies are in the same direction, yet the studies were carried out in three different countries, and instigated by three different sources (government, academia, and industry). Further, the results are in accord with similar findings wherein chemical carcinogens have been found to be mutagenic. Our conclusion is that these three studies, taken together, do provide some evidence that exposure of workers to industrial levels of vinyl chloride is positively associated with an increased frequency of abnormal lymphocyte cells. Any hypothesized links from this conclusion to an association between vinyl chloride exposure and birth defects or fetal wastage would be more credible had the cells examined been germ cells rather than lymphocytes. Our conclusion that there is "some evidence" would be altered to there is "strong evidence" if we could be assured that the control groups were similar to the exposed groups.

3. Excess Fetal Wastage

It is reasonable to hypothesize that a chemical which is associated with excess chromosome aberrations in workers regularly exposed to the chemical could result in a detectable amount of fetal wastage or birth defects in the workers offspring. This hypothesis certainly deserves investigation even though human chromosome studies to date have been done only on surrogate lymphocyte cells instead of actual germ cells.

Purchase et al. [12] included in their 1975 paper on chromosomal aberrations a brief description of a follow-up study to check whether any genetic effects could be induced in the germ cells:

> . . . Fifteen male mice per treatment group were exposed to levels of 30,000, 10,000, and 3,000 p.p.m. of V.C.M. for 6 hours a day on five consecutive days, and an examination for dominant lethal effects in two females mated with each male for 8 consecutive weeks was carried out. There was no significant increase in the number of early deaths per implantation compared with a control group exposed to air alone, indicating that V.C.M. does not produce dominant lethal mutations in mice even at these exceptionally high levels.
>
> It appears, therefore, that the mutagenic effects of vinyl chloride, expressed as chromosomal aberrations in lymphocytes, do not occur in the germ cells. The reason for this could well be that active metabolites of vinyl chloride are responsible for the toxic effects and these do not reach the testis. The potential danger of mutagenic effects on the fetus via the sperm does not therefore seem to exist.

This study was carried out by Imperial Chemical Industries, Limited. The authors' conclusions would be more forceful had they included numerical data on numbers of offspring, deaths, litter sizes, and the size of the control group. For instance, even though no significant increases were found, was there a trend (or lack thereof) with increasing V.C.M. level?

The only human epidemiological study of possible excess fetal wastage in fetal offspring of male vinyl chloride workers is by Infante et al. [13]. This study was carried out at least in part by the Division of Surveillance of NIOSH. The study was published in Lancet in April of 1976 as an Occasional Survey. The treatment groups consisted of an exposed group of 95 V.C.M. polymerisation workers and a control group of 158 rubber and P.V.C. fabrication workers. Paternal age, pregnancy outcome, and estimates for the time of conception of all pregnancies were ascertained by interviewing each of the 95 + 158 workers in October 1974. The authors state that

> . . . No interviews were conducted with workers' wives and no data were obtained concerning maternal age, except indirectly through paternal age.

The authors gave no information on the distribution of workers' reported recall of time intervals since pregnancies. Such information would be useful in assessing the validity of this study, since it is well known that the reliability of recall of past events decreases with time elapsed since the events.

For each worker the date of first employment in his job category was determined from company records. The reported numbers of conceptions and fetal deaths for each worker were then partitioned into those occurring prior to date of first employment and those occurring subsequent to this date. Part of the control group had been matched as a group to the V.C.M. workers by age, so that the average ages of the control and exposed groups were fairly comparable as of October 1974. It appears from reading this paper that unmarried workers or workers whose wives did not become pregnant over the time span of the study were culled out, although the authors do not specifically so state. The following results obtained:

	Prior to Husband's Employment*		Subsequent to Husband's Employment*	
	Control	Exposed	Control	Evposed
Number of Families	95	70	113	62
Mean Paternal Age at Conception (years)	23.0	26.4	30.4	30.2
Number of Pregnancies	159	148	273	139
Number of Fetal Deaths	11	15	24	23
Crude Fetal Death Rate (percent)	6.9	10.1	8.8	16.5
Age-adjusted Fetal Death Rate (percent)	6.9	6.1	8.8	15.8

The authors state that,

> Since fetal loss is known to increase with ascending parental age, the fetal death-rates for the primary V.C.M. exposure group were age-adjusted to the control group.

The exposed group prior to husband's employment was age-adjusted to the paternal age distribution of the control group prior to husband's employment, with a similar age adjustment subsequent to husband's employment. And this accounts for the last line of the above table. Mantel and Haenszel [14] had developed a method for testing hypotheses on age-adjusted rates. This

*The original paper uses the terms, prior to and subsequent to husband's exposure, rather than husband's employment.

was used by the authors to compare the rates, 8.8 percent and 15.8 percent, for the control and exposed groups subsequent to husband's employment, and the difference was found by them to be just significant at the 5 percent level ($\chi^2 = 4.00$, df = 1, $P < 0.05$). Next, they compared the adjusted rates, 6.1 percent and 15.8 percent, for the exposed group prior to and subsequent to husband's employment, and this difference was also significant ($\chi^2 = 5.51$, df = 1, $P < 0.02$). They found no significant difference in a similar comparison of the rates, 8.8 percent and 6.9 percent, for the control group. This method of analysis, however, is grossly in error, and is irrelevant to the conclusions drawn by the authors that,

> . . . The increased fetal mortality among wives of workers subsequent to V.C.M. exposure now raises serious scientific and public-health concern for the possible genetic risks of vinyl chloride to man.

The authors' analytical methods are invalid since the Mantel-Haenszel test requires that the two rates being compared be independent, and this is not the case, for instance, when the 6.1 percent and 15.8 percent adjusted rates are compared. For the 6.1 percent is based on the 70 families in the exposed group prior to husbands' employment, while the 15.9 percent is based on 62 families in the exposed group subsequent to husband's employment. These two groups (prior to and subsequent to husbands' employment) overlap, since they have fathers in common. By elementary probability theory the number of fathers common to both these groups is at least 37 = 70 + 62 - 95, and so the two groups cannot be independent.

The methods used by the authors to test significance are inappropriate since pregnancies are clustered--clustered in families. Thus, for the 6.1 percent versus 15.8 percent comparison of adjusted rates, the sample sizes are not 148 and 139, the numbers of pregnancies, but are instead 70 and 62, the numbers of workers. The χ^2 test tacitly but incorrectly takes the sample sizes to be 148 and 139 when in reality they are less than half these amounts, and this gives an overly optimistic impression of precision. More appropriate would be the use of t-tests as in [9], but even these are not directly applicable because of the above mentioned overlap between groups.

The misleading conclusions drawn by the authors were brought about through the selection and use of their control group. The age-adjustment procedures used changed the crude fetal death rate in the exposed group, prior to husbands' employment, from 10.1 percent to 6.1 percent, while only changing the rate subsequent to husbands' employment from 16.5 percent to 15.8 percent. The crude rates, 10.1 percent and 16.5 percent, were not significantly different. The authors, however, compared the adjusted rates, 6.1 percent and 15.8 percent, and found this difference to be significant. The peculiar behavior of the age-adjustment procedure moved Paddle [15] to write:

> . . . The assertion in the paper by Dr. Infante and his colleagues . . . that "a significant excess of fetal loss was observed among wives following exposure to V.C.M." is such as to have justified much

more complete presentation. Any assertion of such importance should at least be supported by a specification of the methods of data collection, and a tabulation of the raw data before analysis.

The subject being spontaneous abortion, the use of a questionnaire, and the ensuing low response-rates, can be viewed sympathetically, but must detract from the accuracy of the study. The data are presented only after an age-adjustment procedure which behaves very misleadingly. A crude percentage of 10.1 for a sample whose average age is 26.4 is adjusted violently downwards to 6.1, while a figure of 16.5 for a sample of average age 30.2 is only reduced marginally to 15.8.

Infante and his colleagues, in a reply [16] to Paddle, gave the distribution (shown below) of pregnancies and fetal deaths by paternal age for the control and exposure groups both prior to and subsequent to husbands' employment. From this it was clear that the age-adjustment procedure for the exposed group prior to employment was greatly affected by the much younger paternal age distribution of the control group. The problem is that, though the control group was matched by age to the exposed group at the time of the study, which corresponds to "subsequent to employment," this is no guarantee that the two groups would be matched by paternal age prior to employment. The difference between average paternal ages for the control group for subsequent and prior to exposure was 30.4 - 23.0 = 7.4 years, while that for the exposed group was 30.2 - 26.4 = 3.8 years, about half as much, and this is precisely the reason why the control group as constituted is inadequate, and even misleading, for this study.

Paternal Age	Prior to Husband's Employment				Subsequent to Husband's Employment			
	Control		Exposed		Control		Exposed	
<20	2/31	(6.5)	0/7	(0)	0/1	(0)	0/0	(-)
20-24	4/80	(5.0)	2/44	(4.5)	4/43	(9.3)	3/22	(13.6)
25-29	4/38	(10.5)	7/56	(12.5)	3/87	(3.4)	11/48	(22.9)
30-34	1/6	(16.7)	5/27	(18.5)	7/87	(8.0)	3/36	(8.3)
>35	0/4	(0)	1/14	(7.1)	10/55	(18.2)	6/33	(18.2)
All Ages	11/159	(6.9)	15/148	(10.1)	24/273	(8.8)	23/139	(16.5)

There are several notable features of this table. Prior to husband's employment the paternal age distribution of pregnancies for the control group: (31, 80, 38, 6, 4), is vastly diff rent from that for the exposed group: (7, 44,

56, 27, 14). This is a reflection of the younger control group, and illustrates again the incomparability of the exposed and control groups. This incomparability is further demonstrated by noting that, of the 95 workers in the exposed group, the wives of 70 (74 percent) became pregnant prior to husband's employment, while only 95 wives of the 158 workers (60 percent) in the control group had been pregnant prior to husband's employment. A chi-square test shows these percentages to be significantly different ($\chi^2 = 4.23$, df = 1, $P < 0.05$). Also, the only substantial difference in the paternal age-specific rates subsequent to husband's employment is in the 25-29 year age group, where the exposed rate is 22.9 percent and the control rate 3.4 percent. But no patterns are discernible in the other age-specific rates and this single difference is not by itself biologically meaningful or interpretable, and so might be considered an anomaly.

The purpose of adjusting rates is to make them comparable. Adjusting a rate r to a population A and another rate s to a population B, and then comparing the adjusted rates r and s, is contrary to the purpose of adjusting rates, and the resulting comparison does not make any sense. But this is precisely what the authors do when they adjust the prior exposed rate to the prior control group, then adjust the subsequent exposed rate to the subsequent control group, and then compare the adjusted rates. When adjusted rates are to be compared the rates should be adjusted to the same population.

The comparisons of rates made by the authors are irrelevant to the hypotheses tested by them and to their corresponding conclusions. For each test group it is anticipated that the subsequent to employment rate should be higher than the prior rate, since the workers get older. The authors compared the rates subsequent to employment between the two test groups, and the rates prior to and subsequent to employment within each test group. What they should have compared is the difference between groups, of the change within groups from prior to employment to subsequent to employment.

It does not seem possible to salvage anything from this study. What the authors should have done was to match the control group to the exposed by age at time of husband's employment, and not at the time of the study. Since all subjects were currently working this proposed matching procedure would automatically ensure they would also be age-matched at the time of the study. Further, efforts should have been made to check, via hospital records, etc., the completeness and accuracy of the pregnancy events as reported by the workers. The analysis should have been limited to those workers whose wives became pregnant both before and after employment. Thus, for each worker the quantity

$$\begin{pmatrix}\text{fetal death rate}\\ \text{after employment}\end{pmatrix} - \begin{pmatrix}\text{fetal death rate}\\ \text{before employment}\end{pmatrix}$$

is defined and calculable. Means and standard deviations of these could then be computed for the control and for the exposed groups, and the difference in means tested by a two-sample t-test.

An animal study conducted by John et al. [17] of the Dow Chemical Company, and published in 1977, is relevant to the question of fetal wastage.

This study evaluated the effects of maternally inhaled vinyl chloride on embryonal and fetal development in mice, rats, and rabbits. Thorough descriptions of the study design, methods, materials and results appear in this paper. The authors' summary is as follows:

> . . . Groups of pregnant CR-1 mice, Sprague-Dawley rats, and New Zealand white rabbits were exposed to 500 ppm of vinyl chloride 7 hr daily during the period of major organiogenesis. Subsequently, other groups of mice were similarly exposed to 50 ppm of vinyl chloride and rats and rabbits were exposed to 2500 ppm of vinyl chloride. While maternal toxicity was observed, vinyl chloride alone did not cause significant embryonal or fetal toxicity and was not teratogenic in any of the species at the concentrations tested. Maternal toxicity was more prominent among mice than among rats and rabbits. Simultaneous exposure of some of the pregnant animals to vinyl chloride by inhalation plus 15 percent ethanol in the drinking water resulted in toxic effects greater than those associated with exposure to vinyl chloride alone in the three species. The maternal toxicity was enhanced to an extent greater than the embryotoxicity.

Our conclusion is that there is no scientific evidence of excess fetal wastage in offspring of male vinyl chloride workers; also we conclude that there is fairly good evidence of no teratogenic effects from maternally inhaled vinyl chloride in mice, rats and rabbits at rather high levels; we conclude that there is some evidence that there are no dominant lethal effects from paternally inhaled vinyl chloride in mice at very high levels.

4. Birth Defects in Communities

The earliest paper on the subject of excess community birth defects and vinyl chloride was published by Infante [18] in 1976. This study was initiated at the request of the Industrial Union Department of the AFL-CIO. Dr. Infante studied birth defects over the four years 1970-73 in the three Ohio cities (Ashtabula, Avon Lake and Painesville) with polyvinyl chloride production facilities. No two of these three index cities were in the same county, and the author used two sets of controls: the balance of the county for each of the index cities, and the state of Ohio as a whole. The author found that there were statistically significant excess birth defects in each of the three index cities, based on statewide controls; and that of these, two (Avon Lake and Painesville) were statistically significant based on balance of county controls.

As we have stated several times previously, it is essential to the validity of a study that the control groups be chosen to be as similar as is feasible to the groups under test. Comparing a city to a state or to the balance of a county is improper since such control groups have large rural components, and it is well known that urban-rural differences are substantial

and could conceivably contribute differentially to birth defects. Apparently Infante is aware of this, since he states:

> On the basis of population size, three other county-city combinations were then matched to each of the study area county-city combinations and malformation rates were computed for each city and balance of the county, as done previously for the study areas. The differences in the frequency of malformations between the balance of the counties and the cities were not significant.

But this is simply a repetition of a result obtained by improper methods, and does not deal with the crucial issue of having similar control groups. What should be done is a comparison of malformation rates in the three cities with malformation rates in nearby cities of similar size.

The author next focuses on specific birth defects. In consideration of this he writes:

> Malformation rates were then computed for nine* cities in the vicinity of the index communities that were most similar in size to the index communities. In the surrounding cities, two of nine* had significantly greater numbers of malformations than expected. One community, Geneva, which is twelve miles from Ashtabula, and a second community, North Ridgeville, eight miles from Avon Lake, had rates of 25 and 27 malformations/1,000 live births, respectively. These data are shown in Table 3.

These surrounding cities would form much better control groups than those used by the autnor for comparison with the index cities, so we have re-analyzed the data using these cities as controls. The results are shown below. We find it incredible that Dr. Infante did not perform or report this same analysis.

Area	Cases	Births	Rate/1,000	χ^2	P
Ashtabula	33	1,900	17.4	0.02	< 0.90
Two Surrounding Cities	23	1,429	16.1		
Avon Lake	15	738	20.3	3.18	< 0.10
Three Surrounding Cities	149	12,330	12.1		
Painesville	25	1,381	18.1	22.57	< 0.001
Five Surrounding Cities	44	7,762	5.7		

*Actually malformation rates were computed for ten surrounding cities instead of nine.

This more proper analysis shows that only one of the three index cities (Painesville) had a statistically significant ($P < 0.05$) excess of birth defects during the four-year period 1970-73.

The above excerpt continues:

> . . . Since North Ridgeville was proximate to Avon Lake, data for the former were combined with those from the three primary cities being studied, and the occurrence of specific malformations was compared to the expected, which was based on the state average over the period of 1970-73. Table 4 shows data for observed versus expected defects and relative risks for specific malformations.

The author then concentrates on specific malformations for the three index cities plus North Ridgeville. No further reference is made by him to the remaining nine surrounding cities. The city of Mentor, Ohio, was listed as one of the ten surrounding cities and, though this study does not so state, Mentor is closer to the index city of Painesville than North Ridgeville is to Avon Lake. Yet Mentor was not included along with North Ridgeville in subsequent analyses. The malformation rate/1,000 for Mentor was 7.23, while that for North Ridgeville was 27.26. In our judgment the inclusion of North Ridgeville with the index cities is reprehensible--and neither North Ridgeville nor Mentor should be pooled with the index cities. The author states that

> . . . Significant excesses were observed for defects of the central nervous system, upper alimentary tract, genital organs, and club-foot. Because of the severity of the defects involved, the greatest cause for concern appears to be defects of the central nervous system.

With the exception of central nervous system defects, these specific malformation excesses were not broken down for the individual four cities. Observed and expected figures for CNS defects are shown, though, for each of the four cities among live and stillbirths, with expected numbers based on statewide figures. Of the six independent rates for the three index cities, two are significantly excessive. These are the CNS rate for live births in Painesville, and the CNS rate for stillbirths in Painesville. Since only pooled data for all four cities are shown for the other specific anomalies, it is impossible to determine from this study the extent to which these figures may be biased by inclusion of North Ridgeville.

The author concludes:

> The results of the findings suggest that mothers living in communities with PVC-production facilities gave birth to an excess number of children with congenital malformations as compared to the expected based on the state average or based on the experience in the balance of the counties in which these cities are located.
>
> . . . An excess number of central nervous system defects was observed among stillbirths and live births

from the index cities, with the exception of Avon Lake. Most of the excess, however, was attributable primarily to Painesville and secondarily to a community located proximate to Avon Lake, North Ridgeville.

. . . Since many underlying factors could be responsible for the mutagenic and/or teratogenic and carcinogenic mechanisms involved, these preliminary findings obviously do not link polyvinyl chloride production with the increased occurrence of congenital malformations and central nervous system tumors, but indicate the need for further study of possible contributing factors.

A further study was in fact carried out through the Birth Defects Monitoring Program (BDMP) of the Center for Disease Control, and reported in Lancet in 1975 by Edmonds et al. [19]. Two hospitals participating in the BDMP are located in cities with polymerisation facilities: one in Painesville, Ohio, and the other in Pottstown, Pennsylvania.

. . . C.N.S.-malformation rates for white infants born in these two hospitals in 1970-74 were compared with the rates for white infants in each state. No increase was seen in the Pennsylvania hospital, but an increase . . . was noted in the Painesville hospital for the total time 1970-74.

The excess in Painesville was pursued for further study:

. . . 30 controls, the first normal white infant born before and after each case, were selected from the hospital birth registry. Medical records for cases and controls were reviewed to confirm the diagnosis and to obtain, among other data, the parents' occupation and residence at the time of the infant's birth. In addition, parents of 14 of the affected children were interviewed about previous occupations and residences.

The study revealed that none of the interviewed parents of affected infants had ever worked at either of the two P.V.C.-polymerisation plants in Painesville (1 set of parents could not be located, but records show they did not work at these plants at the time of their infant's birth); 2 of the fathers of controls had worked at one of the plants at the time of their infant's births. None of the parents in either group lived within 2 miles of the two plants. The chi-square test of significance was used in comparing the distances from residence and work-place of mothers and fathers to the P.V.C. plants for cases and

> controls. Comparisons were made at distances of 1 to 10 miles, in 1-mile increments. A significantly larger proportion of control mothers than case mothers worked (including housewives) within a 10-mile radius of the P.V.C. plant, at the 95% confidence level. This is probably a chance occurrence among multiple comparisons.
>
> . . . The Ohio Department of Health study [18] is the only report that has suggested that vinyl chloride causes birth defects in man. Although the follow-up study reported here confirmed a moderate increase in C.N.S. malformations in Painesville, Ohio, no association was found with vinyl-chloride exposure.

The initial comparisons in this study of city hospital rates versus statewide rates are in our opinion, as we have said before, not appropriate, and could be misleading. The within-hospital controls obtained by taking normal children born just before and just after the case births, though, is a well-accepted and generally good procedure for obtaining an appropriate control group for the second phase of this study.

A paper by Infante et al. [20] of the Division of Surveillance of NIOSH appeared in 1976. This paper, titled "Carcinogenic, Mutagenic and Teratogenic Risks Associated with Vinyl Chloride," attempts to summarize the evidence for and against vinyl chloride. No new studies or data appear herein. The authors were apparently unaware of the article by Edmonds et al. [19] discussed above, since they state:

> With regard to the teratogenicity of VC, observations of a significant excess of children born with birth defects were reported among populations residing proximate to VC polymerisation facilities. Additional epidemiologic study is needed to determine whether a repeated pattern of excessive numbers of chilren born with birth defects can be observed in other communities with VC polymerisation facilities.

Some light is shed, in [20], on the inclusion of North Ridgeville with the three index PVC cities studied by Infante in [18]:

> . . . North Ridgeville is the only community shown which does not have a PVC polymerisation facility. It was included in the analysis because it is located contiguous to Avon Lake and because it had a high incidence of children born with birth defects . . .

This statement also explains why Mentor, which is closer to Painesville than North Ridgeville to Avon Lake, was not included in the analysis--Mentor had a small incidence of children born with birth defects.

The summary paper [20] by Infante et al. also discusses the findings of the earlier paper [13] by Infante et al. on excess fetal mortality

for wives of workers exposed to VC. They present data purporting to show that excess fetal mortality exists for such wives, and moreover persists even when wives with two or more fetal deaths are excluded. However, their conclusions are based on an age-adjustment procedure which, as described in the previous section, is inappropriate and misleading.

Another study on birth defects and vinyl chloride by Edmonds [21] appeared in the 1976 Proceedings of a Conference on Women and the Workplace. This conference was sponsored in part by the Society for Occupational and Environmental Health. Edmonds, in this study, recounts his earlier study [19] on Painesville, Ohio, and Pottstown, Pennsylvania, and introduces new data on a similar study done for Kanawna County, West Virginia. A vinyl chloride facility is located in this county, and the county exhibited a significant excess of birth defects in the five-year period 1970-74. A matched control group for the cases was selected from hospital birth records in a manner similar to that described for the previous study [19] of Edmonds et al. Then the cases and controls were compared to see if an association between cases and vinyl chloride exposure of the parents could be discerned. They concluded that

> . . . studies did confirm higher CNS rates than expected during the early 1970's, CNS rates are not significantly different from the U.S. rates at the present time. Occupational histories . . . revealed no difference between the case and the controls in possible work exposure to vinyl chloride monomer. Residential histories showed no difference between the case and controls when compared at varying distances from the polyvinyl chloride plants.

Of the studies [18-21] done on vinyl chloride and birth defects only the one done by Infante [18] shows any association. This association is indirect, and is limited to the city of Painesville, Ohio. A subsequent in-depth study [19] by the Center for Disease Control was unable to establish any association between Painesville CNS cases and parental exposure to vinyl chloride monomer. A similar in-depth study [21] for Kanawna County, West Virginia, also showed no such association. There is no pattern in the available data that suggests an association. Our conclusion therefore is that the available scientific evidence does not indicate any association between vinyl chloride and community birth defects.

5. Summary and Discussion

We have reviewed the available pertinent literature on vinyl chloride and birth defects and fetal wastage. Individual studies in a particular area have been assessed for the strength and validity of their conclusions, and the several studies in each area synthesized, accordingly, by taking into account the consistency, strength, specificity, temporal patterns and coherence of the study results.

In summary, we have c ncluded that, to date, (A) there is some evidence of an association between vinyl chloride and chromosome aberrations in

lymphocyte cells of vinyl chloride workers, (B) there is no evidence of an association between vinyl chloride and excess fetal wastage in wives of VC workers, and (C) there is no evidence of an association between vinyl chloride and excess birth defects in communities with PVC production facilities. This does not mean, of course, that there are no such associations. They may exist, but at levels below our ability to detect them at this time. Monitoring of certain communities with PVC production facilities is in progress at this time, and we believe this monitoring should be continued.

The task of collating the existing literature on vinyl chloride and birth defects, and arriving at general conclusions therefrom, has not been an easy one. The difficulties have been enhanced by the poor quality of many of the study designs, and by inappropriate and misleading statistical methods. The methods of selecting control groups for the epidemiologic studies has been, to say the least, very disturbing. We fervently hope greater efforts will be devoted in future studies to improvement of study methodologies and designs.

6. References

[1] Viola, P., Bigott, A. and Caputo, A.: "Oncogenic Response of Rat Skin, Lungs and Bones to Vinyl Chloride." Cancer Research, 31, 1971.

[2] Maltoni, C. and Lefemine, G.: "Carcinogenic Bioassays of Vinyl Chloride: Current Results." Annals N.Y. Aca. of Sciences, 246, 1975.

[3] Falk, H. and Waxweiler, R.: "Epidemiological Studies of Vinyl Chloride Health Effects in the United States." Proc. Roy. Soc. Med., Occup. Health Section, 69, 1976.

[4] Key, M., Director of NIOSH at that time. Personal communication, 1976.

[5] National Emission Standards for Hazardous Air Pollutants: Proposed Standard for Vinyl Chloride, Federal Register, 40, No. 248, Dec. 1975.

[6] Miller, E. and Miller, J.: in Chemical Mutagens, Principles and Methods for Their Detection (edited by A. Hollaender); Vol. 1, New York, 1971.

[7] Funes-Cravioto, F. et al.: "Chromosome Aberrations in Workers Exposed to Vinyl Chloride." Lancet, Feb. 1975.

[8] Snedecor, G. and Cochran, W.: Statistical Methods, 6th Ed., Iowa State Univ. Press, Ames, 1967.

[9] Ducatman, A., Hirschhorn, K. and Selikoff, I.: "Vinyl Chloride Exposure and Human Chromosome Aberrations." Mutation Research, 31, 1975.

[10] Buckton, K., Jacobs, P., Court Brown, W. and Doll, R.: "A Study of the Chromosome Damage Persisting after X-ray Therapy for Ankylosing Spondylitis." Lancet, 1962.

[11] Hirschhorn, K. and Cohen, M.: "Drug-induced Chromosomal Aberrations." Annals N.Y. Aca. of Sciences, 151, 1968.

[12] Purchase, I., Richardson, C. and Anderson, D.: "Chromosomal and Dominant Lethal Effects of Vinyl Chloride." Lancet, Aug. 1975.

[13] Infante, P. et al.: "Genetic Risks of Vinyl Chloride." Lancet, 1976.

[14] Mantel, N. and Haenszel, W.: "Statistical Aspects of the Analysis of Data from Retrospective Studies of Disease." J. Nat'l. Cancer Inst., 22, 1959.

[15] Paddle, G.: "Genetic Risks of Vinyl Chloride." Lancet, 1976.

[16] Infante, P. et al.: "Genetic Risks of Vinyl Chloride." Lancet, 1976.

[17] John, J., Smith, F., Leong, B. and Schwetz, B.: "The Effects of Maternally Inhaled Vinyl Chloride on Embryonal and Fetal Development in Mice, Rats, and Rabbits." Toxicol. and Appl. Pharmacol., 39, 1977.

[18] Infante, P.: "Oncogenic and Mutagenic Risks in Communities with Polyvinyl Chloride Production Facilities." Annals N.Y. Aca. of Sciences, 271, 1976.

[19] Edmonds, L., Falk, H. and Nissim, J.: "Congenital Malformations and Vinyl Chloride." Lancet, 1975.

[20] Infante, P., Wagoner, J. and Waxweiler, R.: "Carcinogenic, Mutagenic and Teratogenic Risks Associated with Vinyl Chloride." Mutation Res., 41, 1976.

[21] Edmonds, L.: "Birth Defects and Vinyl Chloride." Proc. Conf. on Women and the Workplace, Washington, D.C., 1976.